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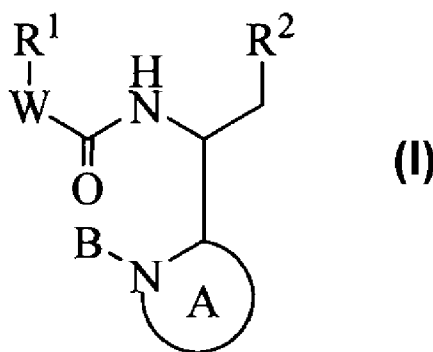
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[Continued on next page]

(54) Title: COMPOUNDS FOR THE TREATMENT OF HIV



(57) Abstract: The invention provides compounds of formula (I): or a salt thereof as described herein. The invention also provides 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.



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Cross Reference to Related Application

This patent application claims the benefit of priority of U.S. application serial No.

5 61/505,032 filed July 6, 2011, which application is hereby incorporated by reference.

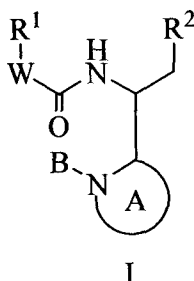
Background of the Invention

Positive-single stranded RNA viruses comprising the *Retroviridae* family include those of the subfamily *Orthoretrovirinae* and genera *Alpharetrovirus*, *Betaretrovirus*, *Gamaretrovirus*,
10 *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
15 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.

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Summary of the Invention

The present invention provides compounds and methods for the treatment of an HIV infection. In one embodiment, the invention provides a compound of the invention which is a compound of formula I:



25

wherein:

A is a 6-membered heteroaryl comprising one or two nitrogens, wherein the 6-membered heteroaryl is substituted with one Z^1 group and optionally substituted with one or more (e.g. 1, 2,
30 or 3) Z^2 groups;

B is absent; or B is $-O^-$ and the nitrogen to which the $-O^-$ group is attached is N^+ ;

W is $-CR^{3a}R^{3b}-$, $-O-$, $-NR^4-$, $-OCR^{3a}R^{3b}-$ or absent;

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^3 groups;

5 R^2 is a 6-membered aryl, 5-membered heteroaryl or 6-membered heteroaryl, wherein any 6-membered aryl, 5-membered heteroaryl or 6-membered heteroaryl of R^2 is optionally substituted with one or more (e.g. 1, 2 or 3) Z^4 groups;

each R^{3a} and R^{3b} is independently selected from H, halogen, (C_1-C_6) alkyl, (C_3-C_7) carbocycle, (C_1-C_3) haloalkyl, (C_1-C_6) heteroalkyl, heteroaryl (C_1-C_6) alkyl-,

10 heterocyclyl (C_1-C_6) alkyl-, $-NR_aR_b$, and $-NR_cCOR_d$, wherein any (C_1-C_6) alkyl of R^{3a} and R^{3b} is optionally substituted with one or more OH groups; or R^{3a} and R^{3b} together with the carbon to which they are attached form a (C_3-C_6) carbocycle;

R^4 is selected from H, (C_1-C_6) alkyl, (C_3-C_6) carbocycle, aryl (C_1-C_6) alkyl- and heteroaryl (C_1-C_6) alkyl-;

15 R_a and R_b 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, aryl, haloaryl, haloheteroaryl, haloheterocycle, (C_1-C_8) haloalkyl and (C_1-C_8) heteroalkyl, or R_a and R_b together with the nitrogen to which they are attached form a 5, 6 or 7-membered heterocycle;

20 each R_c 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-C_8) haloalkyl and (C_1-C_8) heteroalkyl;

each R_d 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, aryl, haloaryl, haloheteroaryl, haloheterocycle, (C_1-C_8) haloalkyl and (C_1-C_8) heteroalkyl;

25 each Z^1 is independently selected from (C_2-C_8) alkyl, (C_2-C_8) alkenyl, (C_2-C_8) alkynyl, (C_3-C_7) carbocycle, aryl, heteroaryl, heterocycle and $-OR_{n1}$, wherein any (C_3-C_7) carbocycle, 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} groups and wherein any (C_1-C_8) alkyl, (C_2-C_8) alkenyl and (C_2-C_8) alkynyl of Z^1 is optionally substituted with one or more (e.g. 1, 2, 3, 4 or 5) Z^{1a} groups;

30 each Z^{1a} is independently selected from (C_3-C_7) carbocycle, aryl, heteroaryl, heterocycle, halogen, $-CN$, $-OR_{n2}$, $-OC(O)R_{p2}$, $-OC(O)NR_{q2}R_{r2}$, $-SR_{n2}$, $-S(O)R_{p2}$, $-S(O)_2OH$, $-S(O)_2R_{p2}$, $-S(O)_2NR_{q2}R_{r2}$, $-NR_{q2}R_{r2}$, $-NR_{n2}COR_{p2}$, $-NR_{n2}CO_2R_{p2}$, $-NR_{n2}CONR_{q2}R_{r2}$, $-NR_{n2}S(O)_2R_{p2}$, $-NR_{n2}S(O)_2OR_{p2}$, $-NR_{n2}S(O)_2NR_{q2}R_{r2}$, NO_2 , $-C(O)R_{n2}$, $-C(O)OR_{n2}$, $-C(O)NR_{q2}R_{r2}$ and

-S(O)₂NR_{n2}COR_{p2}, wherein any (C₃-C₇)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;

each Z^{1b} is independently selected from (C₁-C₈)alkyl, (C₂-C₈)alkenyl and (C₂-C₈)alkynyl, wherein any (C₁-C₈)alkyl, (C₂-C₈)alkenyl and (C₂-C₈)alkynyl of Z^{1b} is optionally substituted with one or more (e.g. 1, 2, 3, 4 or 5) Z^{1c} groups;

each Z^{1c} is independently selected from (C₃-C₇)carbocycle, aryl, heteroaryl, heterocycle, halogen, -CN, -OR_{n3}, -OC(O)R_{p3}, -OC(O)NR_{q3}R_{r3}, -SR_{n3}, -S(O)R_{p3}, -S(O)₂OH, -S(O)₂R_{p3}, -S(O)₂NR_{q3}R_{r3}, -NR_{q3}R_{r3}, -NR_{n3}COR_{p3}, -NR_{n3}CO₂R_{p3}, -NR_{n3}CONR_{q3}R_{r3}, -NR_{n3}S(O)₂R_{p3}, -NR_{n3}S(O)₂OR_{p3}, -NR_{n3}S(O₂NR_{q3}R_{r3}, NO₂, -C(O)R_{n3}, -C(O)OR_{n3}, -C(O)NR_{q3}R_{r3}, haloaryl, haloheteroaryl, haloheterocycle and (C₁-C₈)heteroalkyl;

each Z^{1d} is independently selected from (C₁-C₈)alkyl, (C₂-C₈)alkenyl, (C₂-C₈)alkynyl and (C₁-C₈)haloalkyl;

each R_{n1} is independently selected from (C₁-C₈)alkyl, (C₂-C₈)alkenyl, (C₂-C₈)alkynyl, (C₃-C₇)carbocycle, heterocycle, heteroaryl and aryl, wherein any (C₃-C₇)carbocycle, aryl, heteroaryl and heterocycle of R_{n1} is optionally substituted with one or more (e.g. 1, 2, 3, 4 or 5) Z^{1a} or Z^{1b} groups, and wherein any (C₁-C₈)alkyl, (C₂-C₈)alkenyl and (C₂-C₈)alkynyl of R_{n1} is optionally substituted with one or more (e.g. 1, 2, 3, 4 or 5) Z^{1a} groups;

each R_{n2} is independently selected from H, (C₁-C₈)alkyl, (C₂-C₈)alkenyl, (C₂-C₈)alkynyl, (C₃-C₇)carbocycle, heterocycle, heteroaryl and aryl, wherein any (C₃-C₇)carbocycle, aryl, heteroaryl and heterocycle of R_{n2} is optionally substituted with one or more (e.g. 1, 2, 3, 4 or 5) Z^{1c} or Z^{1d} groups, and wherein any (C₁-C₈)alkyl, (C₂-C₈)alkenyl and (C₂-C₈)alkynyl of R_{n2} is optionally substituted with one or more (e.g. 1, 2, 3, 4 or 5) Z^{1c} groups;

each R_{p2} is independently selected from (C₁-C₈)alkyl, (C₂-C₈)alkenyl, (C₂-C₈)alkynyl, (C₃-C₇)carbocycle, heterocycle, heteroaryl and aryl, wherein any (C₃-C₇)carbocycle, aryl, heteroaryl and heterocycle of R_{p2} is optionally substituted with one or more (e.g. 1, 2, 3, 4 or 5) Z^{1c} or Z^{1d} groups, and wherein any (C₁-C₈)alkyl, (C₂-C₈)alkenyl and (C₂-C₈)alkynyl of R_{p2} is optionally substituted with one or more (e.g. 1, 2, 3, 4 or 5) Z^{1c} groups;

R_{q2} and R_{r2} are each independently selected from H, (C₁-C₈)alkyl, (C₂-C₈)alkenyl, (C₂-C₈)alkynyl, (C₃-C₇)carbocycle, heterocycle, heteroaryl and aryl, wherein any (C₃-C₇)carbocycle, aryl, heteroaryl and heterocycle of R_{q2} or R_{r2} is optionally substituted with one or more (e.g. 1, 2, 3, 4 or 5) Z^{1c} or Z^{1d} groups, and wherein any (C₁-C₈)alkyl, (C₂-C₈)alkenyl and (C₂-C₈)alkynyl of R_{q2} or R_{r2} is optionally substituted with one or more (e.g. 1, 2, 3, 4 or 5) Z^{1c} groups, or R_{q2} and R_{r2} 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;

each R_{n3} is independently selected from H, (C₁-C₈)alkyl, (C₂-C₈)alkenyl, (C₂-C₈)alkynyl, (C₃-C₇)carbocycle, heterocycle, heteroaryl, aryl, haloaryl, haloheteroaryl, haloheterocycle, (C₁-C₈)haloalkyl and (C₁-C₈)heteroalkyl;

each R_{p3} is independently selected from (C₁-C₈)alkyl, (C₂-C₈)alkenyl, (C₂-C₈)alkynyl, (C₃-C₇)carbocycle, heterocycle, heteroaryl, aryl, haloaryl, haloheteroaryl, haloheterocycle, (C₁-C₈)haloalkyl and (C₁-C₈)heteroalkyl;

R_{q3} and R_{r3} are each independently selected from H, (C₁-C₈)alkyl, (C₂-C₈)alkenyl, (C₂-C₈)alkynyl, (C₃-C₇)carbocycle, heterocycle, heteroaryl, aryl, haloaryl, haloheteroaryl, haloheterocycle, (C₁-C₈)haloalkyl and (C₁-C₈)heteroalkyl, or R_{q3} and R_{r3} together with the nitrogen to which they are attached form a 5, 6 or 7-membered heterocycle;

each Z^2 is independently selected from (C₁-C₆)alkyl, (C₁-C₆)haloalkyl, (C₃-C₇)carbocycle, halogen, CN, OH and -O(C₁-C₆)alkyl;

each Z^3 is independently selected from (C₁-C₈)alkyl, (C₂-C₈)alkenyl, (C₂-C₈)alkynyl, (C₃-C₇)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)₂OH, -S(O)₂R_{p4}, -S(O)₂NR_{q4}R_{r4}, -NR_{q4}R_{r4}, -NR_{n4}COR_{p4}, -NR_{n4}CO₂R_{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}, NO₂, -C(O)R_{n4}, -C(O)OR_{n4}, -C(O)NR_{q4}R_{r4} and -B(OR_{q4})(OR_{r4}) wherein any (C₃-C₇)carbocycle, aryl, heteroaryl and heterocycle of Z^3 is optionally substituted with one or more (e.g. 1, 2, 3, 4 or 5) Z^{3a} or Z^{3b} groups, and wherein any (C₁-C₈)alkyl, (C₂-C₈)alkenyl and (C₂-C₈)alkynyl of Z^3 is optionally substituted with one or more (e.g. 1, 2, 3, 4 or 5) Z^{3a} groups;

each Z^{3a} is independently selected from (C₃-C₇)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)₂OH, -S(O)₂R_{p5}, -S(O)₂NR_{q5}R_{r5}, -NR_{q5}R_{r5}, -NR_{n5}COR_{p5}, -NR_{n5}CO₂R_{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}, NO₂, -C(O)R_{n5}, -C(O)OR_{n5}, and -C(O)NR_{q5}R_{r5}, wherein any (C₃-C₇)carbocycle, aryl, heteroaryl and heterocycle of Z^{3a} is optionally substituted with one or more (e.g. 1, 2, 3, 4 or 5) Z^{3c} or Z^{3d} groups;

each Z^{3b} is independently selected from (C₁-C₈)alkyl, (C₂-C₈)alkenyl and (C₂-C₈)alkynyl, wherein any (C₁-C₈)alkyl, (C₂-C₈)alkenyl and (C₂-C₈)alkynyl of Z^{3b} is optionally substituted with one or more (e.g. 1, 2, 3, 4 or 5) Z^{3c} groups;

each Z^{3c} is independently selected from (C₃-C₇)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)₂OH, -S(O)₂R_{p6},

-S(O)₂NR_{q6}R_{r6}, -NR_{q6}R_{r6}, -NR_{n6}COR_{p6}, -NR_{n6}CO₂R_{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}, NO₂, -C(O)R_{n6}, -C(O)OR_{n6}, -C(O)NR_{q6}R_{r6}, haloaryl,
haloheteroaryl, haloheterocycle and (C₁-C₈)heteroalkyl;

each Z^{3d} is independently selected from (C₁-C₈)alkyl, (C₂-C₈)alkenyl, (C₂-C₈)alkynyl, and
5 (C₁-C₈)haloalkyl;

each R_{n4} is independently selected from H, (C₁-C₈)alkyl, (C₂-C₈)alkenyl, (C₂-C₈)alkynyl,
(C₃-C₇)carbocycle, heterocycle, heteroaryl and aryl, wherein any (C₃-C₇)carbocycle, aryl,
heteroaryl and heterocycle of R_{n4} is optionally substituted with one or more (e.g. 1, 2, 3, 4 or 5)
Z^{3a} or Z^{3b} groups, and wherein any (C₁-C₈)alkyl, (C₂-C₈)alkenyl and (C₂-C₈)alkynyl of R_{n4} is
10 optionally substituted with one or more (e.g. 1, 2, 3, 4 or 5) Z^{3a} groups;

each R_{p4} is independently selected from (C₁-C₈)alkyl, (C₂-C₈)alkenyl, (C₂-C₈)alkynyl,
(C₃-C₇)carbocycle, heterocycle, heteroaryl and aryl, wherein any (C₃-C₇)carbocycle, aryl,
heteroaryl, or heterocycle of R_{p4} is optionally substituted with one or more (e.g. 1, 2, 3, 4 or 5)
Z^{3a} or Z^{3b} groups, and wherein any (C₁-C₈)alkyl, (C₂-C₈)alkenyl or (C₂-C₈)alkynyl of R_{p4} is
15 optionally substituted with one or more (e.g. 1, 2, 3, 4 or 5) Z^{3a} groups;

R_{q4} and R_{r4} are each independently selected from H, (C₁-C₈)alkyl, (C₂-C₈)alkenyl, (C₂-
C₈)alkynyl, (C₃-C₇)carbocycle, heterocycle, heteroaryl and aryl, wherein any (C₃-C₇)carbocycle,
aryl, heteroaryl and heterocycle of R_{q4} or R_{r4} is optionally substituted with one or more (e.g. 1,
2, 3, 4 or 5) Z^{3a} or Z^{3b} groups, and wherein any (C₁-C₈)alkyl, (C₂-C₈)alkenyl and (C₂-C₈)alkynyl
20 of R_{q4} or R_{r4} is optionally substituted with one or more (e.g. 1, 2, 3, 4 or 5) Z^{3a} groups, or R_{q4}
and R_{r4} 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^{3a} or Z^{3b} groups;

each R_{n5} is independently selected from H, (C₁-C₈)alkyl, (C₂-C₈)alkenyl, (C₂-C₈)alkynyl,
25 (C₃-C₇)carbocycle, heterocycle, heteroaryl and aryl, wherein any (C₃-C₇)carbocycle, aryl,
heteroaryl and heterocycle of R_{n5} is optionally substituted with one or more (e.g. 1, 2, 3, 4 or 5)
Z^{3c} or Z^{3d} groups, and wherein any (C₁-C₈)alkyl, (C₂-C₈)alkenyl and (C₂-C₈)alkynyl of R_{n5} is
optionally substituted with one or more (e.g. 1, 2, 3, 4 or 5) Z^{3c} groups;

each R_{p5} is independently selected from (C₁-C₈)alkyl, (C₂-C₈)alkenyl, (C₂-C₈)alkynyl,
30 (C₃-C₇)carbocycle, heterocycle, heteroaryl and aryl, wherein any (C₃-C₇)carbocycle, aryl,
heteroaryl and heterocycle of R_{p5} is optionally substituted with one or more (e.g. 1, 2, 3, 4 or 5)
Z^{3c} or Z^{3d} groups, and wherein any (C₁-C₈)alkyl, (C₂-C₈)alkenyl and (C₂-C₈)alkynyl of R_{p5} is
optionally substituted with one or more (e.g. 1, 2, 3, 4 or 5) Z^{3c} groups;

R_{q5} and R_{r5} are each independently selected from H, (C₁-C₈)alkyl, (C₂-C₈)alkenyl, (C₂-C₈)alkynyl, (C₃-C₇)carbocycle, heterocycle, heteroaryl and aryl, wherein any (C₃-C₇)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^{3c} or Z^{3d} groups, and wherein any (C₁-C₈)alkyl, (C₂-C₈)alkenyl and (C₂-C₈)alkynyl of R_{q5} or R_{r5} is optionally substituted with one or more (e.g. 1, 2, 3, 4 or 5) Z^{3c} 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^{3c} or Z^{3d} groups;

each R_{n6} is independently selected from H, (C₁-C₈)alkyl, (C₂-C₈)alkenyl, (C₂-C₈)alkynyl, (C₃-C₇)carbocycle, heterocycle, heteroaryl, aryl, haloaryl, haloheteroaryl, haloheterocycle, (C₁-C₈)haloalkyl and (C₁-C₈)heteroalkyl;

each R_{p6} is independently selected from (C₁-C₈)alkyl, (C₂-C₈)alkenyl, (C₂-C₈)alkynyl, (C₃-C₇)carbocycle, heterocycle, heteroaryl, aryl, haloaryl, haloheteroaryl, haloheterocycle, (C₁-C₈)haloalkyl and (C₁-C₈)heteroalkyl;

R_{q6} and R_{r6} are each independently selected from H, (C₁-C₈)alkyl, (C₂-C₈)alkenyl, (C₂-C₈)alkynyl, (C₃-C₇)carbocycle, heterocycle, heteroaryl, aryl, haloaryl, haloheteroaryl, haloheterocycle, (C₁-C₈)haloalkyl and (C₁-C₈)heteroalkyl, or R_{q6} and R_{r6} together with the nitrogen to which they are attached form a 5, 6 or 7-membered heterocycle;

each Z^4 is independently selected from (C₁-C₈)alkyl, (C₂-C₈)alkenyl, (C₂-C₈)alkynyl, (C₃-C₇)carbocycle, aryl, heteroaryl, heterocycle, halogen, -CN, -OR_{n8}, -OC(O)R_{p8}, -OC(O)NR_{q8}R_{r8}, -SR_{n8}, -S(O)R_{p8}, -S(O)₂OH, -S(O)₂R_{p8}, -S(O)₂NR_{q8}R_{r8}, -NR_{q8}R_{r8}, -NR_{n8}COR_{p8}, -NR_{n8}CO₂R_{p8}, -NR_{n8}CONR_{q8}R_{r8}, -NR_{n8}S(O)₂R_{p8}, -NR_{n8}S(O)₂OR_{p8}, -NR_{n8}S(O)₂NR_{q8}R_{r8}, NO₂, -C(O)R_{n8}, -C(O)OR_{n8}, and -C(O)NR_{q8}R_{r8}, wherein any (C₃-C₇)carbocycle, aryl, heteroaryl and heterocycle of Z^4 is optionally substituted with one or more (e.g. 1, 2, 3, 4 or 5) Z^{4c} or Z^{4d} groups and wherein any (C₁-C₈)alkyl, (C₂-C₈)alkenyl and (C₂-C₈)alkynyl of Z^4 is optionally substituted with one or more (e.g. 1, 2, 3, 4 or 5) Z^{4c} groups;

each Z^{4c} is independently selected from (C₃-C₇)carbocycle, aryl, heteroaryl, heterocycle, halogen, -CN, -OR_{n9}, -OC(O)R_{p9}, -OC(O)NR_{q9}R_{r9}, -SR_{n9}, -S(O)R_{p9}, -S(O)₂OH, -S(O)₂R_{p9}, -S(O)₂NR_{q9}R_{r9}, -NR_{q9}R_{r9}, -NR_{n9}COR_{p9}, -NR_{n9}CO₂R_{p9}, -NR_{n9}CONR_{q9}R_{r9}, -NR_{n9}S(O)₂R_{p9}, -NR_{n9}S(O)₂OR_{p9}, -NR_{n9}S(O)₂NR_{q9}R_{r9}, NO₂, -C(O)R_{n9}, -C(O)OR_{n9}, -C(O)NR_{q9}R_{r9}, haloaryl, haloheteroaryl, haloheterocycle and (C₁-C₈)heteroalkyl;

each Z^{4d} is independently selected from (C₁-C₈)alkyl, (C₂-C₈)alkenyl, (C₂-C₈)alkynyl and (C₁-C₈)haloalkyl;

each R_{n8} is independently selected from H, (C₁-C₈)alkyl, (C₂-C₈)alkenyl, (C₂-C₈)alkynyl, (C₃-C₇)carbocycle, heterocycle, heteroaryl and aryl, wherein any (C₃-C₇)carbocycle, aryl, heteroaryl and heterocycle of R_{n8} is optionally substituted with one or more (e.g. 1, 2, 3, 4 or 5) Z^{4c} or Z^{4d} groups, and wherein any (C₁-C₈)alkyl, (C₂-C₈)alkenyl or (C₂-C₈)alkynyl of R_{n8} is optionally substituted with one or more (e.g. 1, 2, 3, 4 or 5) Z^{4c} groups;

each R_{p8} is independently selected from (C₁-C₈)alkyl, (C₁-C₆)haloalkyl, (C₂-C₈)alkenyl, (C₂-C₈)alkynyl, (C₃-C₇)carbocycle, heterocycle, heteroaryl and aryl, wherein any (C₃-C₇)carbocycle, aryl, heteroaryl and heterocycle of R_{p8} is optionally substituted with one or more (e.g. 1, 2, 3, 4 or 5) Z^{4c} or Z^{4d} groups, and wherein any (C₁-C₈)alkyl, (C₂-C₈)alkenyl and (C₂-C₈)alkynyl of R_{p8} is optionally substituted with one or more (e.g. 1, 2, 3, 4 or 5) Z^{4c} groups;

R_{q8} and R_{r8} are each independently selected from H, (C₁-C₈)alkyl, (C₂-C₈)alkenyl, (C₂-C₈)alkynyl, (C₃-C₇)carbocycle, heterocycle, heteroaryl and aryl, wherein any (C₃-C₇)carbocycle, aryl, heteroaryl and heterocycle of R_{q8} or R_{r8} is optionally substituted with one or more (e.g. 1, 2, 3, 4 or 5) Z^{4c} or Z^{4d} groups, and wherein any (C₁-C₈)alkyl, (C₂-C₈)alkenyl and (C₂-C₈)alkynyl of R_{q8} or R_{r8} is optionally substituted with one or more (e.g. 1, 2, 3, 4 or 5) Z^{4c} groups, or R_{q8} and R_{r8} 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;

each R_{n9} is independently selected from H, (C₁-C₈)alkyl, (C₂-C₈)alkenyl, (C₂-C₈)alkynyl, (C₃-C₇)carbocycle, heterocycle, heteroaryl, aryl, haloaryl, haloheteroaryl, haloheterocycle, (C₁-C₈)haloalkyl and (C₁-C₈)heteroalkyl;

each R_{p9} is independently selected from (C₁-C₈)alkyl, (C₂-C₈)alkenyl, (C₂-C₈)alkynyl, (C₃-C₇)carbocycle, heterocycle, heteroaryl, aryl, haloaryl, haloheteroaryl, haloheterocycle, (C₁-C₈)haloalkyl and (C₁-C₈)heteroalkyl; and

R_{q9} and R_{r9} are each independently selected from H, (C₁-C₈)alkyl, (C₂-C₈)alkenyl, (C₂-C₈)alkynyl, (C₃-C₇)carbocycle, heterocycle, heteroaryl, aryl, haloaryl, haloheteroaryl, haloheterocycle, (C₁-C₈)haloalkyl and (C₁-C₈)heteroalkyl; or R_{q9} and R_{r9} together with the nitrogen to which they are attached form a 5, 6 or 7-membered heterocycle;

or a salt thereof.

The invention also provides a pharmaceutical composition comprising a compound of formula I or a pharmaceutically acceptable salt thereof, in combination with a pharmaceutically acceptable carrier.

The invention also provides a method for treating (e.g. preventing, mediating or inhibiting) 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.

5 The invention also provides a method for treating (e.g. preventing, mediating or 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.

10 The invention also provides a method for treating (e.g. preventing, mediating or inhibiting) 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.

The invention also 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
15 combination with a therapeutically effective amount of one or more additional therapeutic agents selected from the group consisting 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
20 other drugs for treating HIV, and combinations thereof.

The invention also provides a compound of formula I, or a pharmaceutically acceptable salt thereof for use in medical therapy (e.g. for use in treating (e.g. preventing, mediating or inhibiting) 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
25 human)).

The invention also provides a compound of formula I, or a pharmaceutically acceptable salt thereof for use in the manufacture of a medicament for treating (e.g. preventing, mediating or inhibiting) 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
30 human).

The invention also provides a compound of formula I, or a pharmaceutically acceptable salt thereof, for use in the prophylactic or therapeutic treatment (e.g. prevention, mediation or

inhibition) 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.

The invention also provides a compound of formula I, or a pharmaceutically acceptable salt thereof, for use in the prophylactic or therapeutic treatment (e.g. prevention, mediation or inhibition) of a *Retroviridae* virus infection or an HIV virus infection.

The invention also provides the use of a compound of formula I, or a pharmaceutically acceptable salt thereof, for the manufacture of a medicament for treating (e.g. preventing, mediating or inhibiting) a *Retroviridae* virus infection or an HIV virus infection.

The invention also provides processes and intermediates disclosed herein that are useful for preparing compounds of formula I or salts thereof.

Detailed Description of the Invention

Definitions

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

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

“Alkyl” is hydrocarbon containing primary, secondary or tertiary atoms. For example, an alkyl group can have 1 to 20 carbon atoms (*i.e.*, (C₁-C₂₀)alkyl), 1 to 10 carbon atoms (*i.e.*, (C₁-C₁₀)alkyl), 1 to 8 carbon atoms (*i.e.*, (C₁-C₈)alkyl) or 1 to 6 carbon atoms (*i.e.*, (C₁-C₆) alkyl). Examples of suitable alkyl groups include, but are not limited to, methyl (Me, -CH₃), ethyl (Et, -CH₂CH₃), 1-propyl (*n*-Pr, *n*-propyl, -CH₂CH₂CH₃), 2-propyl (*i*-Pr, *i*-propyl, -CH(CH₃)₂), 1-butyl (*n*-Bu, *n*-butyl, -CH₂CH₂CH₂CH₃), 2-methyl-1-propyl (*i*-Bu, *i*-butyl, -CH₂CH(CH₃)₂), 2-butyl (*s*-Bu, *s*-butyl, -CH(CH₃)CH₂CH₃), 2-methyl-2-propyl (*t*-Bu, *t*-butyl, -C(CH₃)₃), 1-pentyl (*n*-pentyl, -CH₂CH₂CH₂CH₂CH₃), 2-pentyl (-CH(CH₃)CH₂CH₂CH₃), 3-pentyl (-CH(CH₂CH₃)₂), 2-methyl-2-butyl (-C(CH₃)₂CH₂CH₃), 3-methyl-2-butyl (-CH(CH₃)CH(CH₃)₂), 3-methyl-1-butyl (-CH₂CH₂CH(CH₃)₂), 2-methyl-1-butyl (-CH₂CH(CH₃)CH₂CH₃), 1-hexyl (-CH₂CH₂CH₂CH₂CH₂CH₃), 2-hexyl (-CH(CH₃)CH₂CH₂CH₂CH₃), 3-hexyl (-CH(CH₂CH₃)(CH₂CH₂CH₃)), 2-methyl-2-pentyl (-C(CH₃)₂CH₂CH₂CH₃), 3-methyl-2-pentyl (-CH(CH₃)CH(CH₃)CH₂CH₃), 4-methyl-2-pentyl (-CH(CH₃)CH₂CH(CH₃)₂), 3-methyl-3-pentyl (-C(CH₃)(CH₂CH₃)₂), 2-methyl-3-pentyl (-CH(CH₂CH₃)CH(CH₃)₂), 2,3-dimethyl-2-butyl (-C(CH₃)₂CH(CH₃)₂), 3,3-dimethyl-2-butyl (-CH(CH₃)C(CH₃)₃), and octyl (-CH₂)₇CH₃). “Alkyl” also refers to a saturated, branched or straight

chain hydrocarbon radical having two monovalent radical centers derived by the removal of two hydrogen atoms from the same or two different carbon atoms of a parent alkane. For example, an alkyl group can have 1 to 10 carbon atoms (*i.e.*, (C₁-C₁₀)alkyl), or 1 to 6 carbon atoms (*i.e.*, (C₁-C₆)alkyl) or 1-3 carbon atoms (*i.e.*, (C₁-C₃)alkyl). Typical alkyl radicals include, but are not limited to, methylene (-CH₂-), 1,1-ethyl (-CH(CH₃)-), 1,2-ethyl (-CH₂CH₂-), 1,1-propyl (-CH(CH₂CH₃)-), 1,2-propyl (-CH₂CH(CH₃)-), 1,3-propyl (-CH₂CH₂CH₂-), 1,4-butyl (-CH₂CH₂CH₂CH₂-), and the like.

“Alkenyl” is a straight or branched hydrocarbon containing primary, secondary or tertiary carbon atoms with at least one site of unsaturation, *i.e.* a carbon-carbon, *sp*² double bond. For example, an alkenyl group can have 2 to 20 carbon atoms (*i.e.*, C₂-C₂₀ alkenyl), 2 to 8 carbon atoms (*i.e.*, C₂-C₈ alkenyl), or 2 to 6 carbon atoms (*i.e.*, C₂-C₆ alkenyl). Examples of suitable alkenyl groups include, but are not limited to, ethylene or vinyl (-CH=CH₂), allyl (-CH₂CH=CH₂) and 5-hexenyl (-CH₂CH₂CH₂CH₂CH=CH₂).

“Alkynyl” is a straight or branched hydrocarbon containing primary, secondary or tertiary carbon atoms with at least one site of unsaturation, *i.e.* a carbon-carbon, *sp* triple bond. For example, an alkynyl group can have 2 to 20 carbon atoms (*i.e.*, C₂-C₂₀ alkynyl), 2 to 8 carbon atoms (*i.e.*, C₂-C₈ alkynyl), or 2 to 6 carbon atoms (*i.e.*, C₂-C₆ alkynyl). Examples of suitable alkynyl groups include, but are not limited to, acetylenic (-C≡CH), propargyl (-CH₂C≡CH), and the like.

The term “halo” or “halogen” as used herein refers to fluoro, chloro, bromo and iodo.

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 (C₁-C₆)haloalkyl is a (C₁-C₆)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.

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 (C₁-C₆)alkyl.

The term “aryl” as used herein refers to a single aromatic ring or a multiple condensed ring system. 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. 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. 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 aryl 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.

“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(C₁-C₆)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.

The term “heteroaryl” as used herein refers to a single aromatic ring or a multiple condensed ring system. 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 heteroaryls (e.g. naphthyridinyl), heterocycles, (e.g. 1, 2, 3, 4-tetrahydronaphthyridinyl), carbocycles (e.g. 5,6,7,8-tetrahydroquinolyl) or aryls (e.g. indazolyl) to form a multiple condensed ring system. 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. It is 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, thiazolyl, furyl, oxadiazolyl, thiadiazolyl, quinolyl, isoquinolyl, benzothiazolyl, benzoxazolyl, indazolyl, quinoxalyl, quinazolyl, 5,6,7,8-tetrahydroisoquinolyl benzofuranyl, benzimidazolyl and thianaphthenyl.

The term “heterocyclyl” or “heterocycle” as used herein refers to a single saturated or partially unsaturated ring or a multiple condensed ring system. 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 azetidiny, tetrahydrofuranyl or piperidiny. 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 heterocycles (e.g. decahydronaphthyridiny), carbocycles (e.g. decahydroquinoly) or aryls. The rings of a 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 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 aziridiny, azetidiny, pyrrolidiny, piperidiny, homopiperidiny, morpholiny, thiomorpholiny, piperaziny, tetrahydrofuranyl, dihydrooxazolyl, tetrahydropyranyl, tetrahydrothiopyranyl, 1,2,3,4-tetrahydroquinoly, benzoxaziny, dihydrooxazolyl, chromanyl, 1,2-dihydropyridiny, 2,3-dihydrobenzofuranyl, 1,3-benzodioxolyl and 1,4-benzodioxanyl.

“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(C₁-C₆)alkyl). Heteroarylalkyl groups include, but are not limited to heteroaryl-CH₂-, heteroaryl-CH(CH₃)-, heteroaryl-CH₂CH₂-, 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-thiazolyethan-1-yl, imidazolylmethyl, oxazolylmethyl, thiadiazolylmethyl, etc., 6-membered sulfur, oxygen, and/or nitrogen containing heteroaryls such as pyridinylmethyl, pyridizylmethyl, pyrimidinylmethyl,

pyrazinylmethyl, etc.

“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(C₁-C₆)alkyl). Typical heterocyclylalkyl groups include, but are not limited to heterocyclyl-CH₂-, heterocyclyl-CH(CH₃)-, heterocyclyl-CH₂CH₂-, 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 as tetrahydrofuranylmethyl and pyrrolidinylmethyl, etc., and 6-membered sulfur, oxygen, and/or nitrogen containing heterocycles such as piperidinylmethyl, piperazinylmethyl, morpholinylmethyl, etc.

The term “carbocycle” or “carbocyclyl” refers to a single saturated (*i.e.*, cycloalkyl) or a single partially unsaturated (*e.g.*, cycloalkenyl, cycloalkadienyl, etc.) ring having 3 to 7 carbon atoms (*i.e.* (C₃-C₇)carbocycle). The term “carbocycle” or “carbocyclyl” also includes multiple condensed ring systems (*e.g.* ring systems comprising 2, 3 or 4 carbocyclic rings). Accordingly, carbocycle includes multicyclic carbocycles having 6 to 12 carbon atoms as a bicycle (*e.g.* bicyclo[3.1.0]hexane, bicyclo[2.1.1]hexane), and up to about 20 carbon atoms as a polycycle. Multicyclic carbocycles can be connected to each other via a single carbon atom to form a spiro connection (*e.g.* spiro[4.5]decane, spiro[4.5]decane, etc), via two adjacent carbon atoms to form a fused connection such as a bicyclo [4,5], [5,5], [5,6] or [6,6] system, or 9 or 10 ring atoms arranged as a bicyclo [5,6] or [6,6] system (*e.g.* 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.

“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(C₁-C₆)alkyl). Typical carbocyclyl alkyl groups include, but are not limited to carbocyclyl-CH₂-, carbocyclyl-CH(CH₃)-, carbocyclyl-CH₂CH₂-, 2-(carbocyclyl)ethan-1-yl, and the like, wherein the “carbocyclyl” portion includes any of the carbocyclyl groups described above.

5 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.

 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
10 halo substituent. Such a range includes one halo substituent on the heteroaryl group to complete halogenation of the heteroaryl group.

 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
15 complete halogenation of the heterocycle group.

 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
20 as falling within the scope of the present invention.

 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 term “chiral” refers to molecules which have the property of non-superimposability
25 of the mirror image partner, while the term “achiral” refers to molecules which are superimposable on their mirror image partner.

 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.

 “Diastereomer” refers to a stereoisomer with two or more centers or axes of chirality and
30 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.

“Enantiomers” refer to two stereoisomers of a compound which are non-superimposable mirror images of one another.

It is to be understood that certain variables of formula I may have alternative orientations. For example, the $-\text{OCR}^{3a}\text{R}^{3b}$ - variable for W may be oriented in a manner in which the $\text{CR}^{3a}\text{R}^{3b}$ group is connected to the carbonyl of formula I and the O is connected to the R^1 group of formula I and also in a manner in which the $\text{CR}^{3a}\text{R}^{3b}$ group is connected to the R^1 group of formula I and the O is connected to the carbonyl of formula I. In one embodiment of the invention the $\text{CR}^{3a}\text{R}^{3b}$ group is connected to the carbonyl of formula I and the O is connected to the R^1 group of formula I. In another embodiment of the invention the $\text{CR}^{3a}\text{R}^{3b}$ group is connected to the R^1 group of formula I and the O is connected to the carbonyl of formula I.

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.

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. Many organic compounds exist in optically active forms, *i.e.*, they have the ability to rotate the plane of plane-polarized light. In describing an optically active compound, the prefixes (D and L) or (R and S) are used to denote the absolute configuration of the molecule about its chiral center(s). The prefixes d and l or (+) and (-) are employed to designate the sign of rotation of plane-polarized light by the compound, with (-) or l meaning that the compound is levorotatory. A compound prefixed with (+) or d is dextrorotatory. For a given chemical structure, these stereoisomers are identical except that they are mirror images of one another. A specific stereoisomer may also be referred to as an enantiomer, and a mixture of such isomers is often called an enantiomeric mixture. A 50:50 mixture of enantiomers is referred to as a racemic mixture or a racemate, which may occur where there has been no stereoselection or stereospecificity in a chemical reaction or process. The terms “racemic mixture” and “racemate” refer to an equimolar mixture of two enantiomeric species, devoid of optical activity.

Protecting Groups

In the context of the present invention, protecting groups include prodrug moieties and chemical protecting groups.

“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.

5 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
10 analytical tools. Chemically protected intermediates may themselves be biologically active or inactive.

Protected compounds may also exhibit altered, and in some cases, optimized properties *in vitro* and *in vivo*, such as passage through cellular membranes and resistance to enzymatic degradation or sequestration. In this role, protected compounds with intended therapeutic
15 effects may be referred to as prodrugs. Another function of a protecting group is to convert the parental drug into a prodrug, whereby the parental drug is released upon conversion of the prodrug *in vivo*. Because active prodrugs may be absorbed more effectively than the parental drug, prodrugs may possess greater potency *in vivo* than the parental drug. Protecting groups are removed either *in vitro*, in the instance of chemical intermediates, or *in vivo*, in the case of
20 prodrugs. With chemical intermediates, it is not particularly important that the resulting products after deprotection, *e.g.*, alcohols, be physiologically acceptable, although in general it is more desirable if the products are pharmacologically innocuous.

Protecting groups are available, commonly known and used, and are optionally used to prevent side reactions with the protected group during synthetic procedures, *i.e.* routes or
25 methods to prepare the compounds of the invention. For the most part the decision as to which groups to protect, when to do so, and the nature of the chemical protecting group “PG” will be dependent upon the chemistry of the reaction to be protected against (*e.g.*, acidic, basic, oxidative, reductive or other conditions) and the intended direction of the synthesis. PGs do not need to be, and generally are not, the same if the compound is substituted with multiple PG. In
30 general, PG will be used to protect functional groups such as carboxyl, hydroxyl, thio, or amino groups and to thus prevent side reactions or to otherwise facilitate the synthetic efficiency. The order of deprotection to yield free deprotected groups is dependent upon the intended direction of the synthesis and the reaction conditions to be encountered, and may occur in any order as

determined by the artisan.

Various functional groups of the compounds of the invention may be protected. For example, protecting groups for –OH groups (whether hydroxyl, carboxylic acid, phosphonic acid, or other functions) include “ether- or ester-forming groups”. Ether- or ester-forming groups are capable of functioning as chemical protecting groups in the synthetic schemes set forth herein. However, some hydroxyl and thio protecting groups are neither ether- nor ester-forming groups, as will be understood by those skilled in the art, and are included with amides, discussed below.

A very large number of hydroxyl protecting groups and amide-forming groups and corresponding chemical cleavage reactions are described in Protective Groups in Organic Synthesis, Theodora W. Greene (John Wiley & Sons, Inc., New York, 1991, ISBN 0-471-62301-6) (“Greene”). See also Kocienski, Philip J.; Protecting Groups (Georg Thieme Verlag Stuttgart, New York, 1994), which is incorporated by reference in its entirety herein. In particular Chapter 1, Protecting Groups: An Overview, pages 1-20, Chapter 2, Hydroxyl Protecting Groups, pages 21-94, Chapter 3, Diol Protecting Groups, pages 95-117, Chapter 4, Carboxyl Protecting Groups, pages 118-154, Chapter 5, Carbonyl Protecting Groups, pages 155-184. For protecting groups for carboxylic acid, phosphonic acid, phosphonate, sulfonic acid and other protecting groups for acids see Greene as set forth below.

Stereoisomers

The compounds of the invention may have chiral centers, *e.g.*, chiral carbon or phosphorus atoms. The compounds of the invention thus include racemic mixtures of all stereoisomers, including enantiomers, diastereomers, and atropisomers. In addition, the compounds of the invention 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. In most instances, the desired optical isomer is synthesized by means of stereospecific reactions, beginning with the appropriate stereoisomer of the desired starting material.

It is to be understood that for compounds of the invention 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 of the invention may be greater than 50% a single enantiomer. In another embodiment, a compound of the invention may be at least 51% a single enantiomer. In another embodiment, a compound of the invention may be at least 60% a single enantiomer. In another embodiment, a compound of the invention may be at least 70% a single enantiomer. In another embodiment, a compound of the invention may be at least 80% a single enantiomer. In another embodiment, a compound of the invention may be at least 90% a single enantiomer. In another embodiment, a compound of the invention may be at least 95% a single enantiomer. In another embodiment, a compound of the invention may be at least 98% a single enantiomer. In another embodiment, a compound of the invention may be at least 99% a single enantiomer. In another embodiment, a compound of the invention may be greater than 50% a single diastereomer. In another embodiment, a compound of the invention may be at least 51% a single diastereomer. In another embodiment, a compound of the invention may be at least 60% a single diastereomer. In another embodiment, a compound of the invention may be at least 70% a single diastereomer. In another embodiment, a compound of the invention may be at least 80% a single diastereomer. In another embodiment, a compound of the invention may be at least 90% a single diastereomer. In another embodiment, the compounds of the invention are at least 95% a single diastereomer. In another embodiment, a compound of the invention may be at least 98% a single diastereomer. In another embodiment, a compound of the invention may be at least 99% a single diastereomer.

The compounds of the invention 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. Other examples include keto-enol tautomers of hydroxy heterocycles such as hydroxy quinolines (e.g. 2-hydroxy quinoline and quinolin-2-ones).

Salts and Hydrates

Examples of pharmaceutically acceptable salts of the compounds of the invention 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 hydrogen 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 X is independently selected from H or a C_1-C_4 alkyl group).

For therapeutic use, salts of active ingredients of the compounds of the invention 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 of the invention. All salts, whether or not derived from a physiologically acceptable acid or base, are within the scope of the present invention.

Metal salts typically are prepared by reacting the metal hydroxide with a compound of this invention. 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.

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, typically amines, or to acidic groups. Finally, it is to be understood that the compositions herein comprise compounds of the invention in their un-ionized, as well as zwitterionic form, and combinations with stoichiometric amounts of water as in hydrates.

Also included within the scope of this invention are the salts of the parental compounds with one or more amino acids. Any of the natural or unnatural amino acids are suitable, especially the naturally-occurring amino acids found as protein components, although the amino acid typically is one bearing a side chain with a basic or acidic group, *e.g.*, lysine, arginine or glutamic acid, or a neutral group such as glycine, serine, threonine, alanine, isoleucine, or leucine.

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.

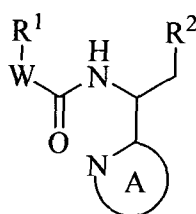
5 Isotopes

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 $-\text{CH}_3$ group may be substituted with $-\text{CD}_3$.

10

Compounds of formula I.

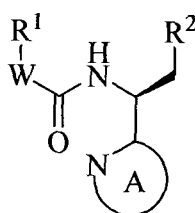
A specific group of compounds of formula I are compounds of formula I':



I'

15 or a salt thereof.

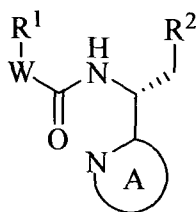
A specific group of compounds of formula I are compounds of formula Ia:



Ia

or a salt thereof.

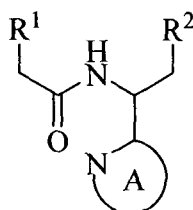
20 Another specific group of compounds of formula I are compounds of formula Ia':



Ia'

or a salt thereof.

Another specific group of compounds of formula I are compounds of formula Ib:

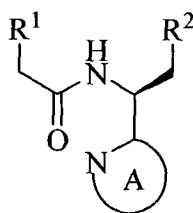


5

Ib

or a salt thereof.

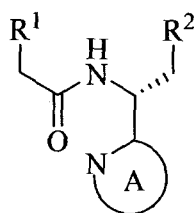
Another specific group of compounds of formula I are compounds of formula Ic:



Ic

10 or a salt thereof.

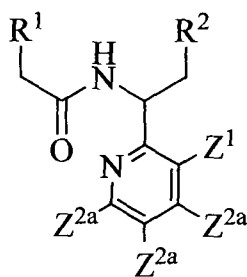
Another specific group of compounds of formula I are compounds of formula Ic':



Ic'

or a salt thereof.

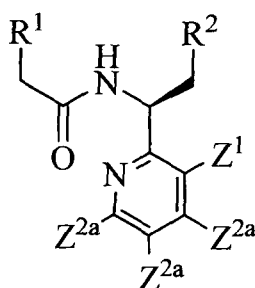
15 Another specific group of compounds of formula I are compounds of formula Id:



Id

wherein each Z^{2a} is independently H or Z^2 , or a salt thereof.

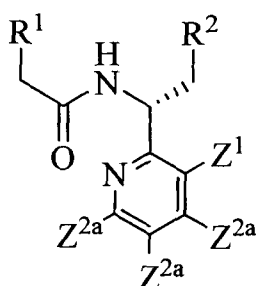
Another specific group of compounds of formula I are compounds of formula Ie:



Ie

5 wherein each Z^{2a} is independently H or Z^2 , or a salt thereof.

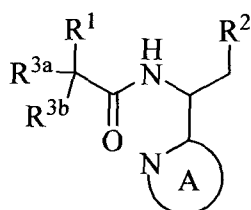
Another specific group of compounds of formula I are compounds of formula Ie':



Ie'

wherein each Z^{2a} is independently H or Z^2 , or a salt thereof.

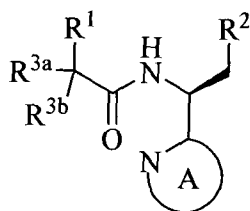
10 Another specific group of compounds of formula I are compounds of formula Ibb:



Ibb

or a salt thereof.

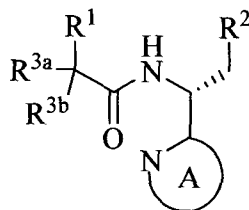
Another specific group of compounds of formula I are compounds of formula Icc:



Icc

or a salt thereof.

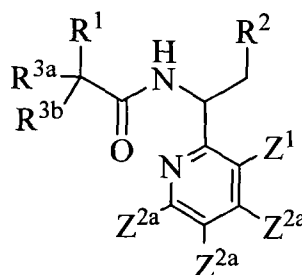
Another specific group of compounds of formula I are compounds of formula Icc':



Icc'

5 or a salt thereof.

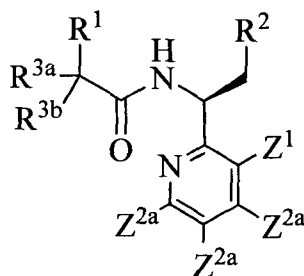
Another specific group of compounds of formula I are compounds of formula Idd:



Idd

wherein each Z^{2a} is independently H or Z^2 , or a salt thereof.

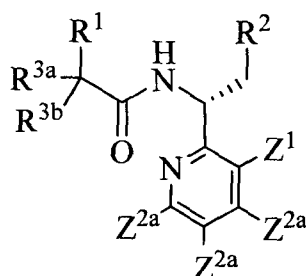
10 Another specific group of compounds of formula I are compounds of formula Iee:



Iee

wherein each Z^{2a} is independently H or Z^2 , or a salt thereof.

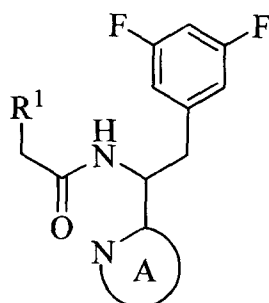
Another specific group of compounds of formula I are compounds of formula Iee':



Iee'

wherein each Z^{2a} is independently H or Z^2 , or a salt thereof.

Another specific group of compounds of formula I are compounds of formula If:

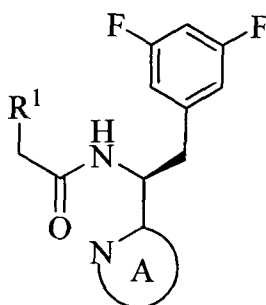


5

If

or a salt thereof.

Another specific group of compounds of formula I are compounds of formula If':

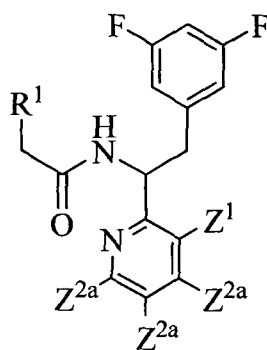


10

If'

or a salt thereof.

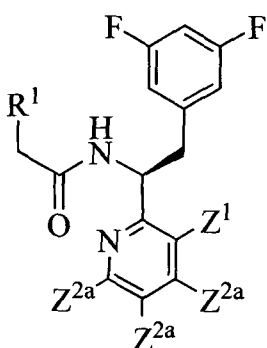
Another specific group of compounds of formula I are compounds of formula Ig:



Ig

wherein each Z^{2a} is independently H or Z^2 , or a salt thereof.

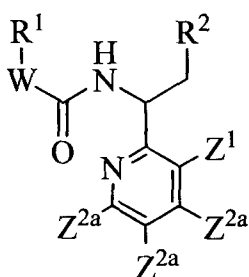
Another specific group of compounds of formula I are compounds of formula Ih.



Ih

wherein each Z^{2a} is independently H or Z^2 , or a salt thereof.

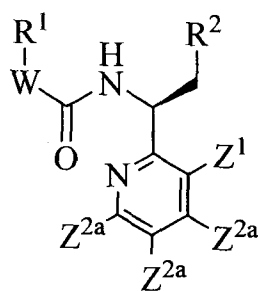
Another specific group of compounds of formula I are compounds of formula Ii:



Ii

wherein each Z^{2a} is independently H or Z^2 , or a salt thereof.

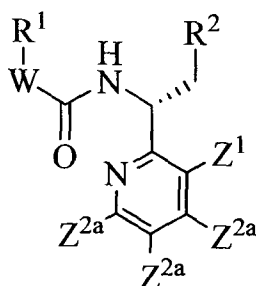
Another specific group of compounds of formula I are compounds of formula Ij:



Ij

wherein each Z^{2a} is independently H or Z^2 , or a salt thereof.

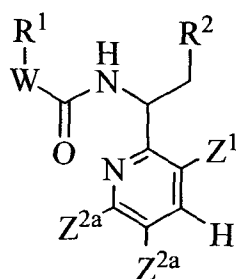
Another specific group of compounds of formula I are compounds of formula Ij':



Ij'

wherein each Z^{2a} is independently H or Z^2 , or a salt thereof.

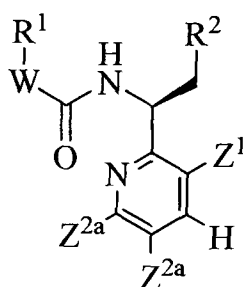
Another specific group of compounds of formula I are compounds of formula Ik:



Ik

wherein each Z^{2a} is independently H or Z^2 , or a salt thereof.

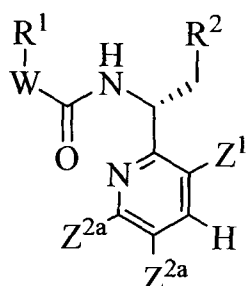
Another specific group of compounds of formula I are compounds of formula Im:



Im

wherein each Z^{2a} is independently H or Z^2 , or a salt thereof.

Another specific group of compounds of formula I are compounds of formula Im':

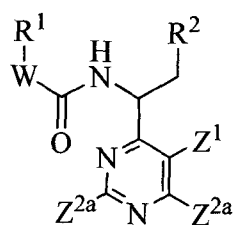


5

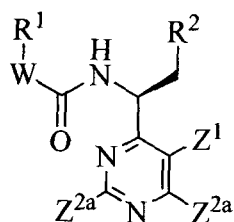
Im'

wherein each Z^{2a} is independently H or Z^2 , or a salt thereof.

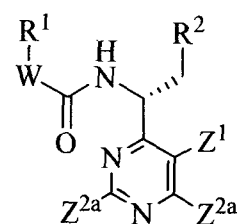
Another specific group of compounds of formula I are compounds of formula In, Io, Io', Ip, Iq, Iq', Ir, Is or Is':



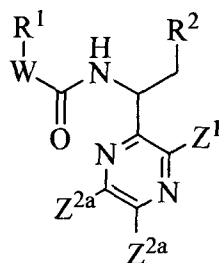
In



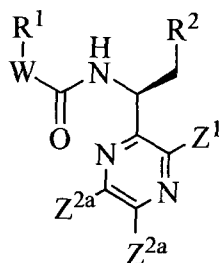
Io



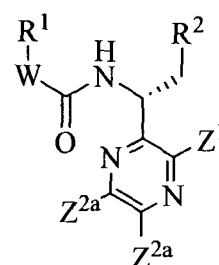
Io'



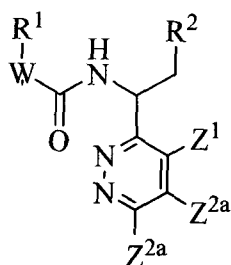
Ip



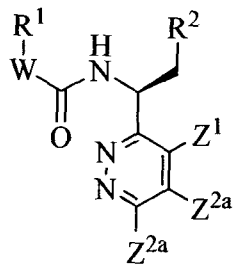
Iq



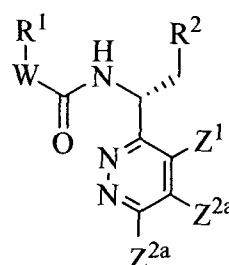
Iq'



Ir



Is

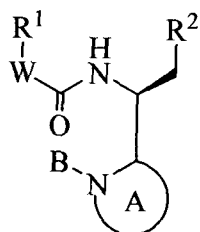


Is'

In

wherein each Z^{2a} is independently H or Z^2 , or a salt thereof.

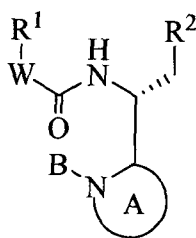
Another specific group of compounds of formula I are compounds of formula It:



It

or a salt thereof.

Another specific group of compounds of formula I are compounds of formula It':



It'

or a salt thereof.

Specific values listed herein below are values for compounds of formula I as well as compounds of sub-formulas of formula I (e.g. formulas I' Ia, Ia', Ib, Ic, Ic', Id, Ie, Ie', Ibb, Icc, Icc', Idd, Iee, Iee, If, If', Ig, Ih, Ii, Ij, Ij', Ik, Im, Im', In, Io, Io', Ip, Iq, Iq', Ir, Is, Is', It and It')

A specific value for W is $\text{CR}^{3a}\text{R}^{3b}$ or NR^4 .

Another specific value for W is $-\text{CR}^{3a}\text{R}^{3b}-$, $-\text{O}-$, $-\text{NR}^4-$ or $-\text{OCR}^{3a}\text{R}^{3b}-$.

Another specific value for W is $-\text{CR}^{3a}\text{R}^{3b}-$, $-\text{OCR}^{3a}\text{R}^{3b}-$ or absent.

10 Another specific value for W is $-\text{CR}^{3a}\text{R}^{3b}-$.

A specific group of compounds of formula I are compounds wherein R^4 is H and, wherein each R^{3a} and R^{3b} is independently selected from H, $(\text{C}_1\text{-C}_3)\text{alkyl}$, $(\text{C}_1\text{-C}_3)\text{haloalkyl}$, NR_aR_b , and $-\text{NR}_c\text{COR}_d$, or R^{3a} and R^{3b} together with the carbon to which they are attached form a $(\text{C}_3\text{-C}_6)\text{carbocycle}$.

15 Another specific value for W is $-\text{CH}_2-$, $-\text{CH}(\text{CH}_3)-$, $-\text{CH}(\text{CH}_2\text{CH}_3)-$, $-\text{CH}(\text{CF}_3)-$, $-\text{CH}(\text{CH}_2\text{CF}_3)-$, $-\text{CH}(\text{CH}_2\text{CHF}_2)-$, $-\text{CH}(\text{NH}_2)-$, $-\text{CH}(\text{NHC}(=\text{O})\text{CH}_3)-$, 1,1-cyclopropyldiyl or $-\text{NH}-$.

Another specific value for W is $-\text{CH}_2-$, $-\text{CH}(\text{CH}_3)-$, $-\text{CH}(\text{NH}_3)-$, $-\text{CH}(\text{NHC}(=\text{O})\text{CH}_3)-$, 1,1-cyclopropyldiyl or $-\text{NH}-$.

20 Another specific value for W is $-\text{CH}_2-$.

A specific group of compounds of formula I are compounds wherein B is absent.

A specific value for R^2 is a 6-membered aryl wherein the 6-membered aryl is optionally substituted with one or more (e.g. 1, 2 or 3) Z^4 groups.

A specific value for Z^4 is $(\text{C}_3\text{-C}_7)\text{carbocycle}$, halogen or $-\text{CN}$.

25 Another specific value for Z^4 is cyclopropyl, fluoro or $-\text{CN}$.

Another specific value for Z^4 is fluoro.

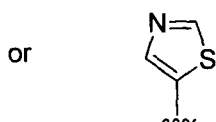
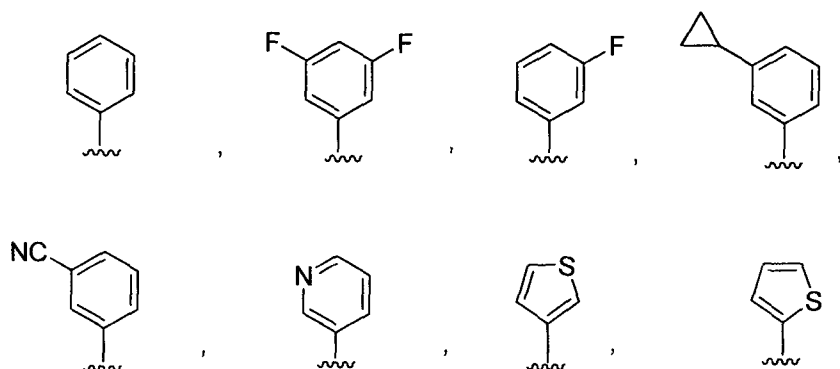
Another specific value for Z^4 is fluoro or chloro.

Another specific value for Z^4 is $(\text{C}_1\text{-C}_8)\text{alkyl}$, $(\text{C}_3\text{-C}_7)\text{carbocycle}$, halogen or OR_{n6} , wherein any $(\text{C}_1\text{-C}_8)\text{alkyl}$ of Z^4 is optionally substituted with one or more halogens.

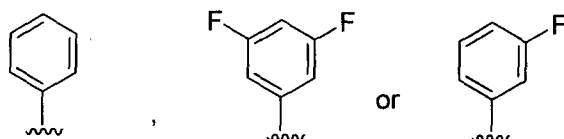
Another specific value for Z^4 is (C₃-C₇)carbocycle, halogen, methyl or -CN.

Another specific value for Z^4 is halogen.

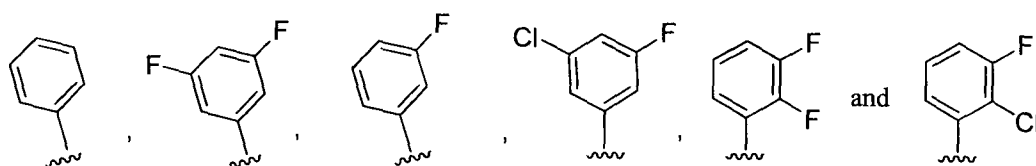
Another specific value for R^2 is:



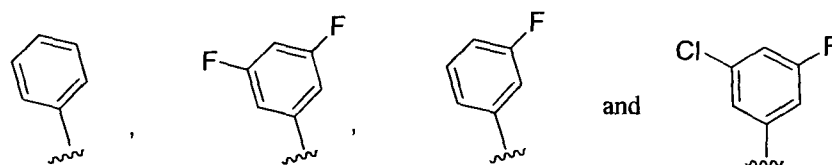
5 Another specific value for R^2 is:



Another specific value for R^2 is:



10 Another specific value for R^2 is:



A specific value for R^1 is heteroaryl or heterocycle, wherein any heteroaryl or heterocycle of R^1 is optionally substituted with one or more Z^3 groups.

Another specific value for R^1 is bicyclic-heteroaryl, tricyclic-heteroaryl, bicyclic-heterocycle or tricyclic-heterocycle, wherein any bicyclic-heteroaryl, tricyclic-heteroaryl, bicyclic-heterocycle or tricyclic-heterocycle, of R^1 is optionally substituted with one or more Z^3 groups.

5 Another specific value for R^1 is 4, 5, 6, 7-tetrahydroindazolyl, 5-oxo-4,5-dihydro-1H-pyrrolo[3,2-b]pyridinyl, 1,4,5,7-tetrahydropyranopyrazolyl, 3-oxo-2,3,4,5,6,7-hexahydro-indazolyl, pyrrolo[2,3-c]pyridinyl, pyrrolo[2,3-b]pyridinyl, 1H-pyrrolo[3,2-c]pyridinyl, 1H-pyrrolo[3,2-b]pyridinyl, benzoimidazolyl, 5-phenyl-pyrazolyl, pyrrolo[3,2-d]pyrimidinyl, 5-oxo-5,6-dihydro-1H-pyrrolo[2,3-c]pyridinyl, 6-oxo-6,7-dihydro-1H-pyrrolo[2,3-b]pyridinyl, 1,7-dihydropyrrolo[3,2-f]indazolyl, 1,6-dihydropyrrolo[2,3-e]indazolyl, 2-oxo-2H-thiazolo[5,4-f]indolyl, 2-oxoindolin-3-yl or indolyl, wherein any 4, 5, 6, 7-tetrahydroindazolyl, 5-oxo-4,5-dihydro-1H-pyrrolo[3,2-b]pyridinyl, 1,4,5,7-tetrahydropyranopyrazolyl, 3-oxo-2,3,4,5,6,7-hexahydro-indazolyl, pyrrolo[2,3-c]pyridinyl, pyrrolo[2,3-b]pyridinyl, 1H-pyrrolo[3,2-c]pyridinyl, 1H-pyrrolo[3,2-b]pyridinyl, benzoimidazolyl, 5-phenyl-pyrazolyl, pyrrolo[3,2-d]pyrimidinyl, 5-oxo-5,6-dihydro-1H-pyrrolo[2,3-c]pyridinyl, 6-oxo-6,7-dihydro-1H-pyrrolo[2,3-b]pyridinyl, 1,7-dihydropyrrolo[3,2-f]indazolyl, 1,6-dihydropyrrolo[2,3-e]indazolyl, 2-oxo-2H-thiazolo[5,4-f]indolyl, 2-oxoindolin-3-yl or indolyl of R^1 is optionally substituted with one or more Z^3 groups.

Another specific value for R^1 is 4,5,6,7-tetrahydroindazolyl or indolyl, wherein any 4,5,6,7-tetrahydroindazolyl or indolyl of R^1 is optionally substituted with one or more Z^3 groups.

Another specific value for R^1 is 4,5,6,7-tetrahydroindazolyl, 5-oxo-4,5-dihydro-1H-pyrrolo[3,2-b]pyridinyl or indolyl, wherein any 4, 5, 6, 7-tetrahydroindazolyl, 5-oxo-4,5-dihydro-1H-pyrrolo[3,2-b]pyridinyl or indolyl of R^1 is optionally substituted with one or more Z^3 groups.

25 Another specific value for R^1 is tricyclic-heteroaryl or tricyclic-heterocycle, wherein any tricyclic-heteroaryl or tricyclic-heterocycle of R^1 is optionally substituted with one or more Z^3 groups.

Another specific value for R^1 is bicyclic-heteroaryl, tricyclic-heteroaryl, bicyclic-heterocycle or tricyclic-heterocycle, wherein any bicyclic-heteroaryl, tricyclic-heteroaryl, bicyclic-heterocycle or tricyclic-heterocycle of R^1 contains at least one partially unsaturated ring, and wherein any bicyclic-heteroaryl, tricyclic-heteroaryl, bicyclic-heterocycle or tricyclic-heterocycle of R^1 is optionally substituted with one or more Z^3 groups.

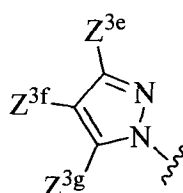
Another specific value for R^1 is tricyclic-heteroaryl or tricyclic-heterocycle, wherein any tricyclic-heteroaryl or tricyclic-heterocycle of R^1 contains one aromatic ring, one partially unsaturated ring, and one fully saturated ring, and wherein any tricyclic-heteroaryl or tricyclic-heterocycle of R^1 is optionally substituted with one or more Z^3 groups.

5 Another specific value for R^1 is bicyclic-heteroaryl, tricyclic-heteroaryl, bicyclic-heterocycle or tricyclic-heterocycle, wherein any bicyclic-heteroaryl, tricyclic-heteroaryl, bicyclic-heterocycle or tricyclic-heterocycle of R^1 contains 5 or more halogen atoms, and wherein any bicyclic-heteroaryl, tricyclic-heteroaryl, bicyclic-heterocycle or tricyclic-heterocycle of R^1 is optionally additionally substituted with one or more Z^3 groups.

10 Another specific value for R^1 is tricyclic-heteroaryl or tricyclic-heterocycle, wherein any tricyclic-heteroaryl or tricyclic-heterocycle of R^1 contains a bridged bicyclic carbocycle or a bridged bicyclic heterocycle, and wherein any tricyclic-heteroaryl or tricyclic-heterocycle of R^1 is optionally substituted with one or more Z^3 groups.

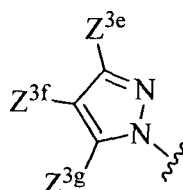
15 Another specific value for R^1 is tricyclic-heteroaryl or tricyclic-heterocycle, wherein any tricyclic-heteroaryl or tricyclic-heterocycle of R^1 contains a spiro-connected bicyclic carbocycle or a spiro-connected bicyclic heterocycle, and wherein any tricyclic-heteroaryl or tricyclic-heterocycle of R^1 is optionally substituted with one or more Z^3 groups.

Another specific value for R^1 is:



20 wherein Z^{3e} , Z^{3f} , and Z^{3g} are each independently selected from H and Z^3 ; or Z^{3e} is H or Z^3 , and Z^{3f} and Z^{3g} together with the carbons to which they are attached form a 5, 6, or 7-membered heterocycle or a 5, 6, or 7-membered carbocycle, which 5, 6, or 7-membered heterocycle or a 5, 6, or 7-membered carbocycle is optionally substituted with one or more Z^3 groups.

Another specific value for R^1 is:



wherein Z^{3e} is H or Z^3 , and Z^{3f} and Z^{3g} together with the carbons to which they are attached form a 5, 6, or 7-membered heterocycle or a 5, 6, or 7-membered carbocycle, which 5, 6, or 7-membered heterocycle or a 5, 6, or 7-membered carbocycle is optionally substituted with one or more Z^3 groups.

5 Another specific value for R^1 is heteroaryl or heterocycle, wherein any heteroaryl or heterocycle of R^1 is optionally substituted with one or more Z^3 groups, provided R^1 does not include indolyl.

Another specific value for R^1 is bicyclic-heteroaryl, tricyclic-heteroaryl, bicyclic-heterocycle or tricyclic-heterocycle, wherein any bicyclic-heteroaryl, tricyclic-heteroaryl, bicyclic-heterocycle or tricyclic-heterocycle, of R^1 is optionally substituted
10 with one or more Z^3 groups, provided R^1 does not include indolyl.

Another specific value for R^1 is bicyclic-heteroaryl, tricyclic-heteroaryl, bicyclic-heterocycle or tricyclic-heterocycle, wherein any bicyclic-heteroaryl, tricyclic-heteroaryl, bicyclic-heterocycle or tricyclic-heterocycle of R^1 contains 5 or more
15 halogen atoms, and wherein any bicyclic-heteroaryl, tricyclic-heteroaryl, bicyclic-heterocycle or tricyclic-heterocycle of R^1 is optionally additionally substituted with one or more Z^3 groups, provided R^1 does not include indolyl.

Another specific value for 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^3
20 groups, provided R^1 does not include indolyl.

A specific value for Z^3 is (C_1-C_8) alkyl, halogen, $-OR_{n4}$, $-NR_{q4}R_{r4}$ or $-NR_{n4}S(O)_2R_{p4}$, wherein any (C_1-C_8) alkyl of Z^3 is optionally substituted with one or more Z^{3a} groups.

Another specific value for Z^3 is (C_1-C_8) alkyl, (C_2-C_8) alkenyl, (C_2-C_8) alkynyl, (C_3-C_7) carbocycle, aryl, halogen, $-CN$, $-OR_{n4}$, $-S(O)_2R_{p4}$, $-NR_{n4}CO_2R_{p4}$, $-NR_{n4}S(O)_2R_{p4}$,
25 $-C(O)R_{n4}$, $-C(O)OR_{n4}$, $-C(O)NR_{q4}R_{r4}$ or $-B(OR_{q4})(OR_{r4})$, wherein any (C_3-C_7) carbocycle and aryl of Z^3 is optionally substituted with one or more (e.g. 1, 2, 3, 4 or 5) Z^{3a} or Z^{3b} groups, and wherein any (C_1-C_8) alkyl, (C_2-C_8) alkenyl and (C_2-C_8) alkynyl of Z^3 is optionally substituted with one or more (e.g. 1, 2, 3, 4 or 5) Z^{3a} groups.

Another specific value for Z^3 is (C_1-C_8) alkyl, (C_2-C_8) alkenyl, (C_2-C_8) alkynyl, (C_3-C_7) carbocycle, aryl, halogen, $-CN$, $-OR_{n4}$, $-S(O)_2R_{p4}$, $-NR_{n4}S(O)_2R_{p4}$, $-S(O)_2NR_{q4}R_{r4}$, $-NR_{q4}R_{r4}$, $-C(O)R_{n4}$, $-C(O)NR_{q4}R_{r4}$ or $-NR_{n4}COR_{q4}$ wherein any (C_3-C_7) carbocycle and aryl of Z^3
30 is optionally substituted with one or more (e.g. 1, 2, 3, 4 or 5) Z^{3a} or Z^{3b} groups, and wherein any

(C₁-C₈)alkyl, (C₂-C₈)alkenyl and (C₂-C₈)alkynyl of Z³ is optionally substituted with one or more (e.g. 1, 2, 3, 4 or 5) Z^{3a} groups

Another specific value for Z³ is methyl, trifluoromethyl, hydroxy, methoxy, benzyloxy, fluoro, -NHSO₂CH₃, 2-hydroxyprop-2yl, difluoromethyl or amino.

5 A specific value for Z^{3a} is halogen.

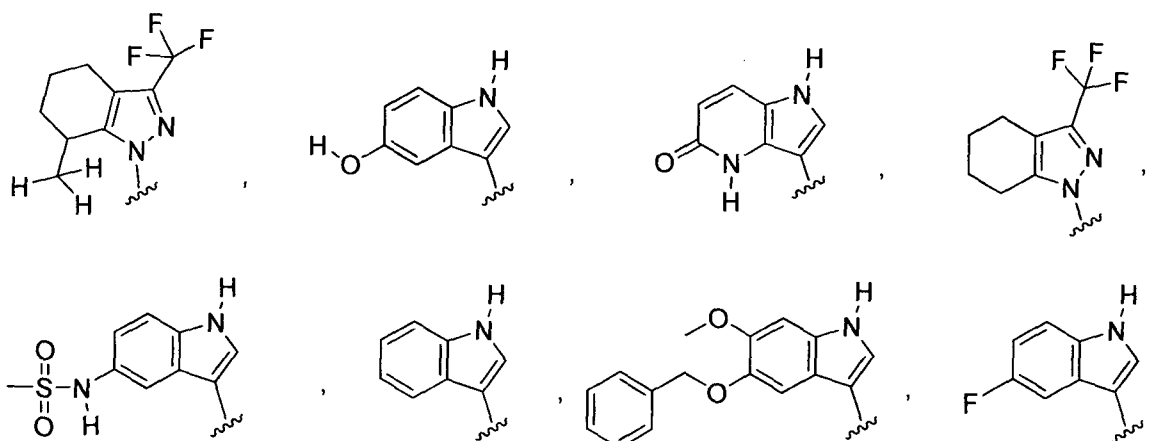
Another specific value for Z^{3a} is halogen and -OR_{n5}.

Another specific value for Z^{3a} is, aryl, heterocycle, halogen, -OR_{n5}, -NR_{q5}R_{r5} or -NR_{n5}CO₂R_{p5}, wherein any aryl, heteroaryl and heterocycle of Z^{3a} is optionally substituted with one or more (e.g. 1, 2, 3, 4 or 5) Z^{3c} or Z^{3d} groups.

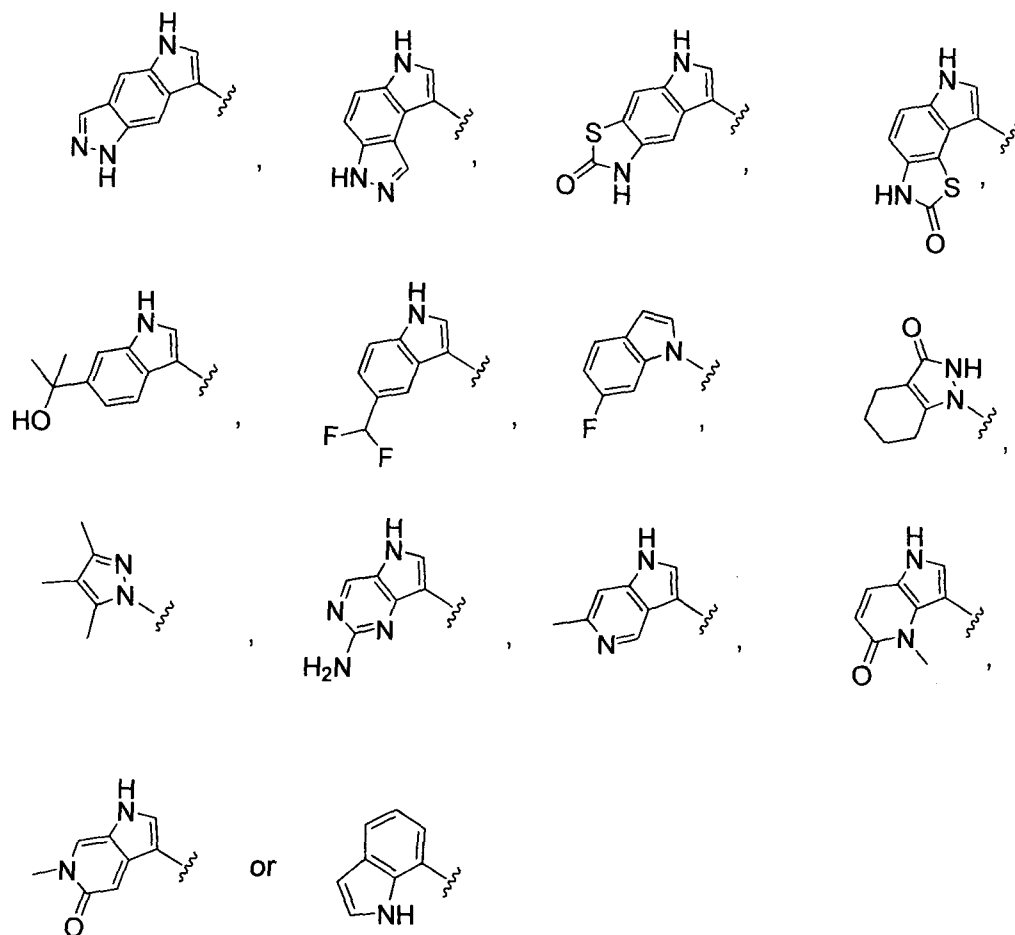
10 Another specific value for Z³ is methyl, trifluoromethyl, hydroxy, methoxy, benzyloxy, fluoro, -NHSO₂CH₃, 2-hydroxyprop-2yl, difluoromethyl or amino.

Another specific value for Z³ is methyl, trifluoromethyl, hydroxy, methoxy, benzyloxy, fluoro or -NHSO₂CH₃.

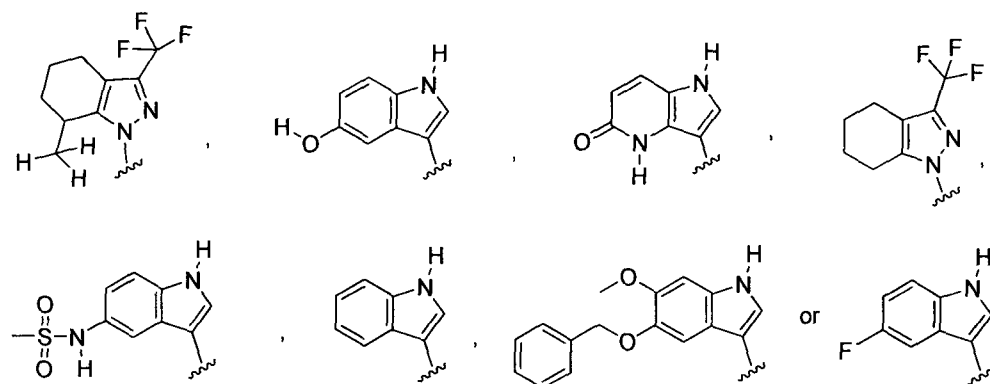
A specific value for R¹ is:



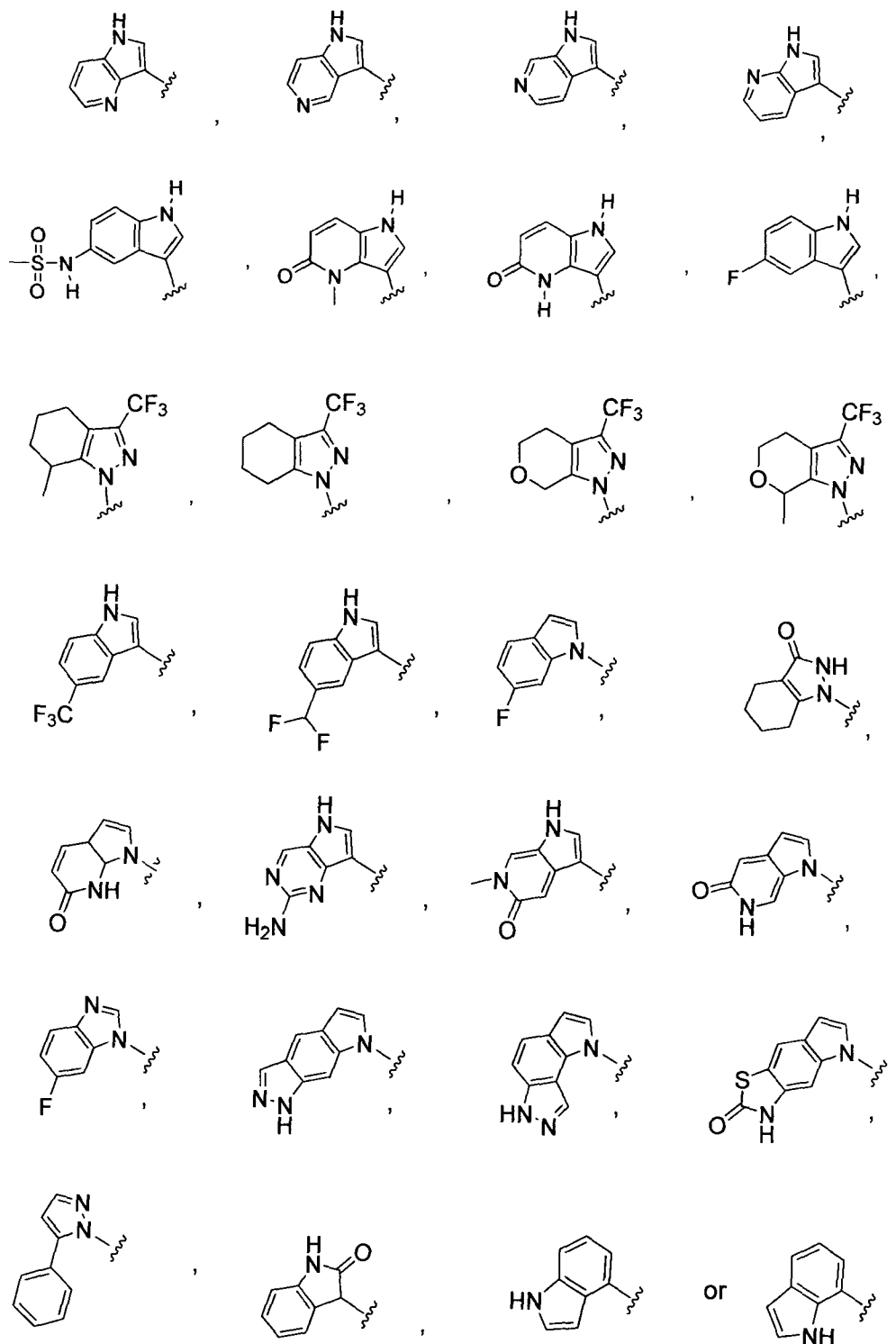
15



Another specific value for R^1 is:

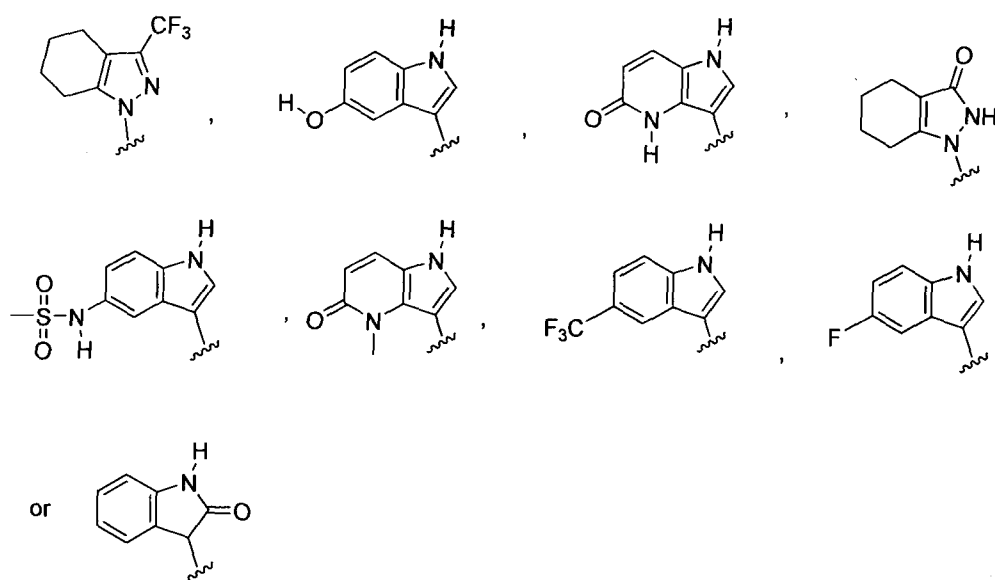


Another specific value for R^1 is:

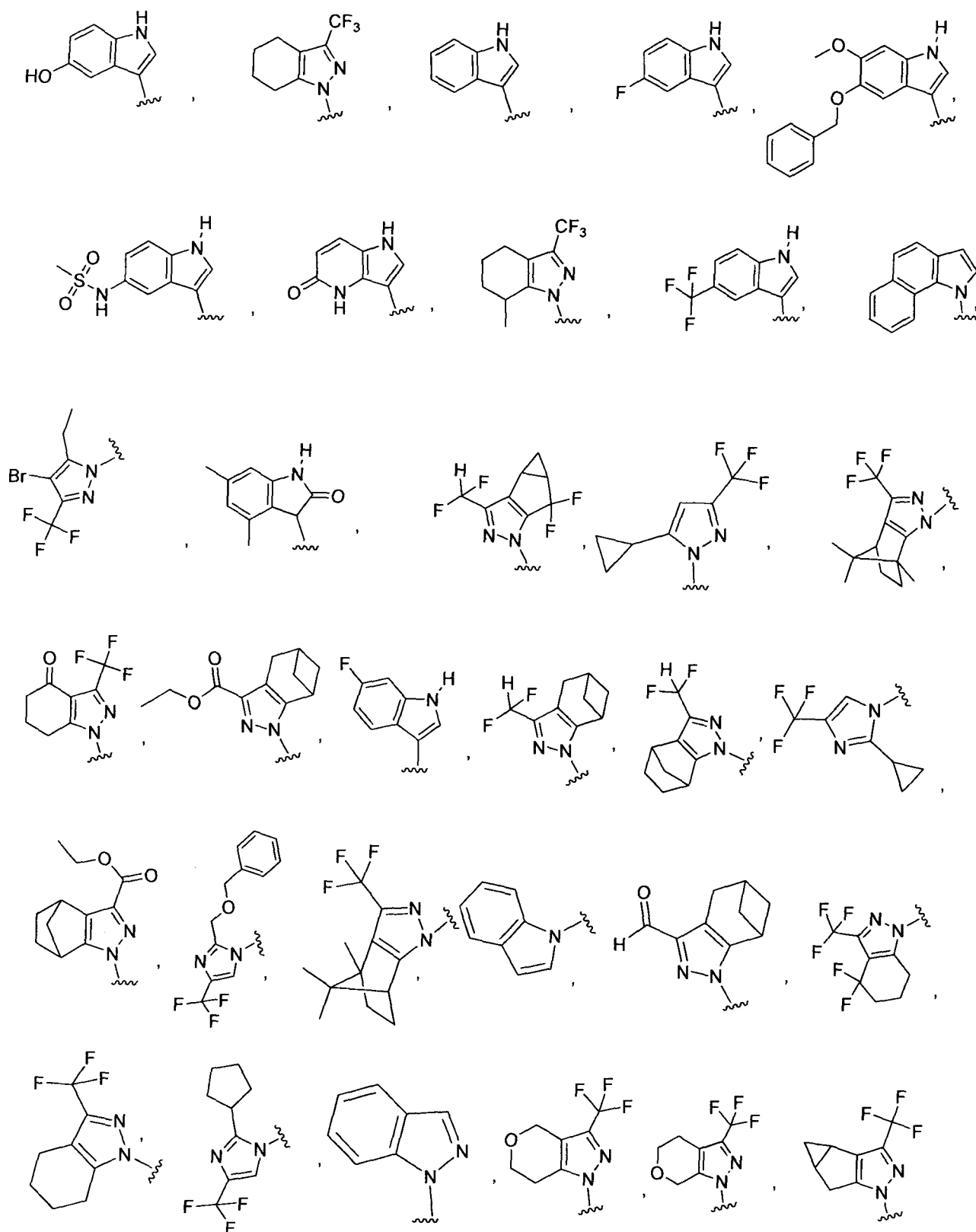


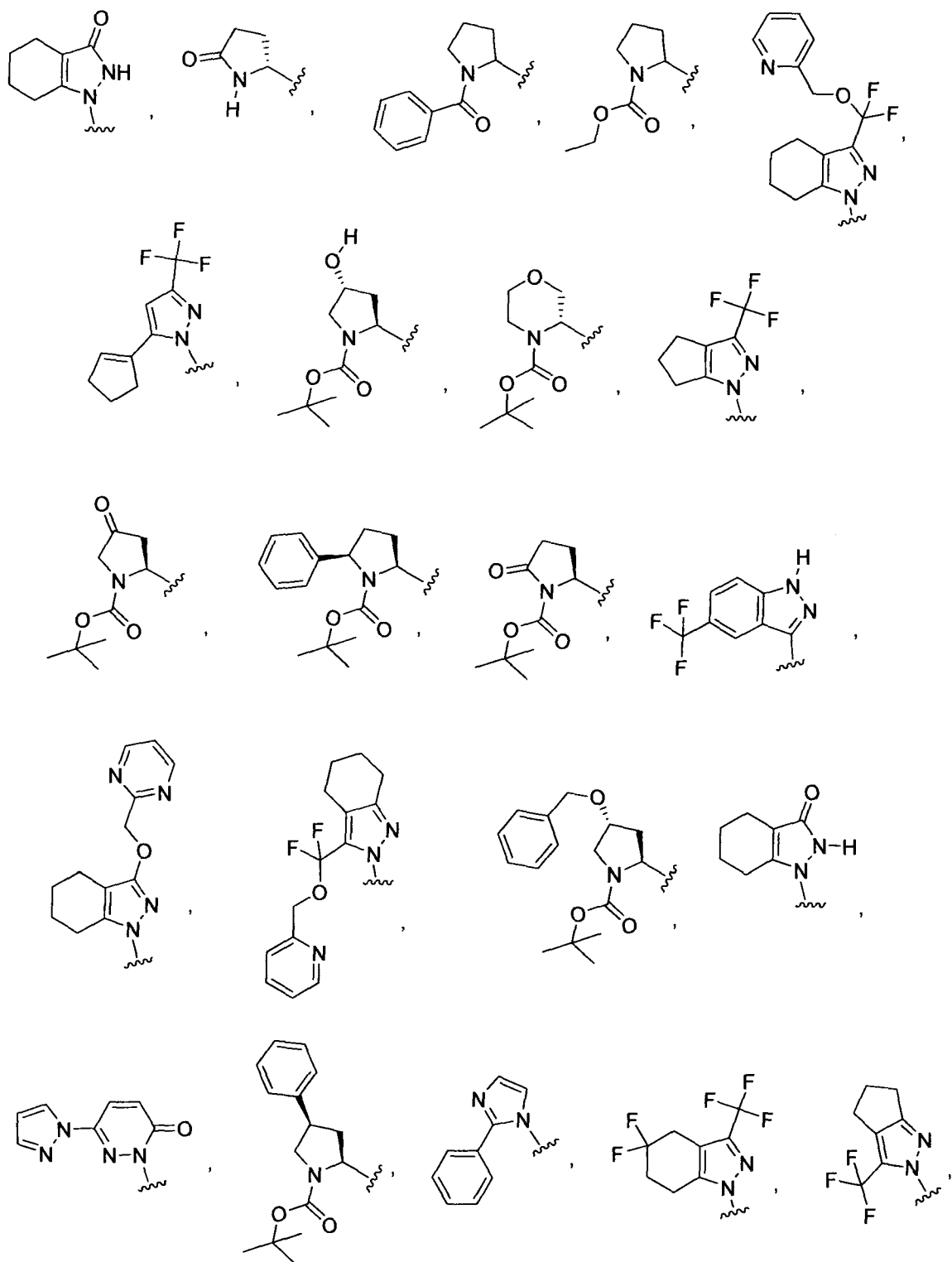
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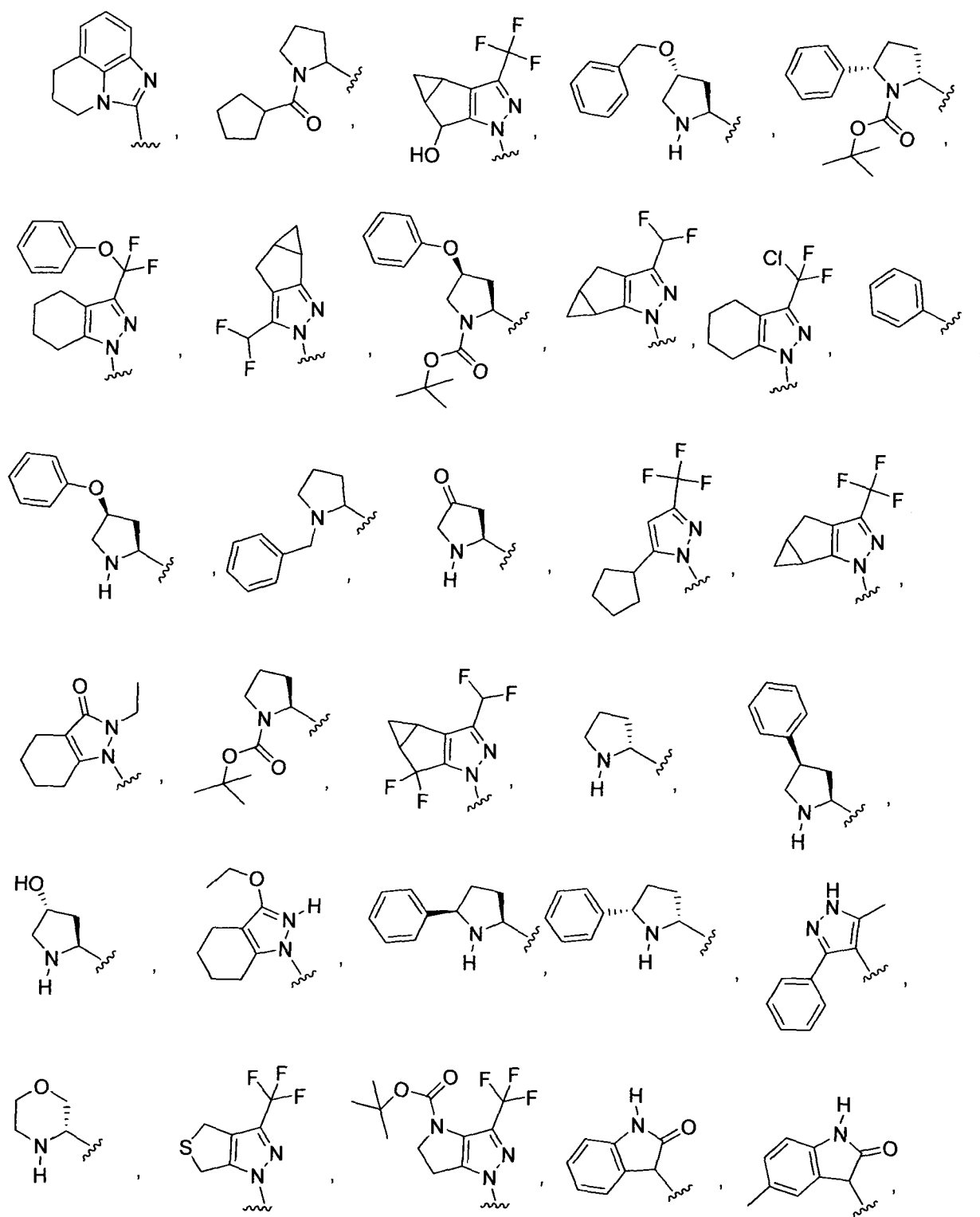
Another specific value for R¹ is:

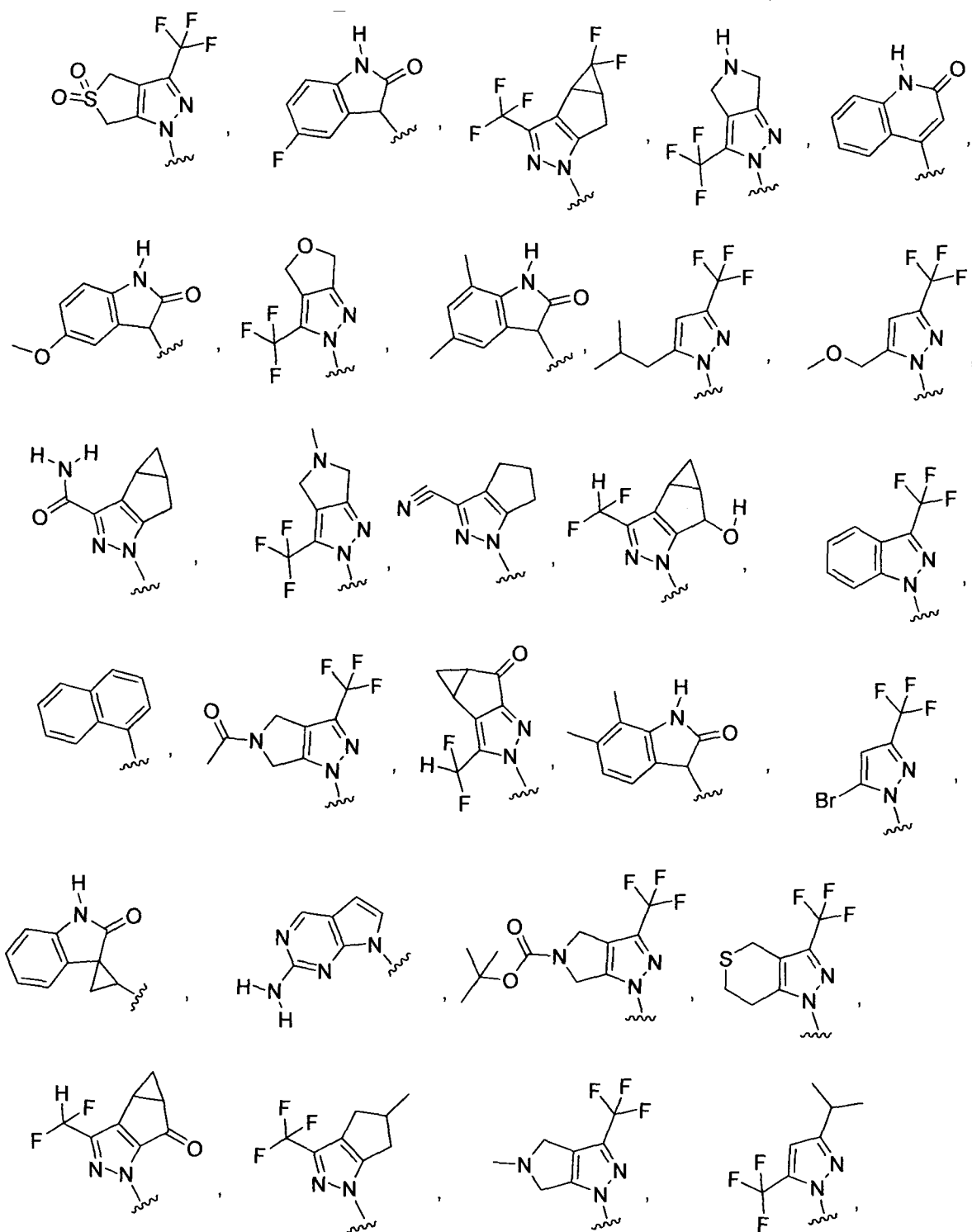


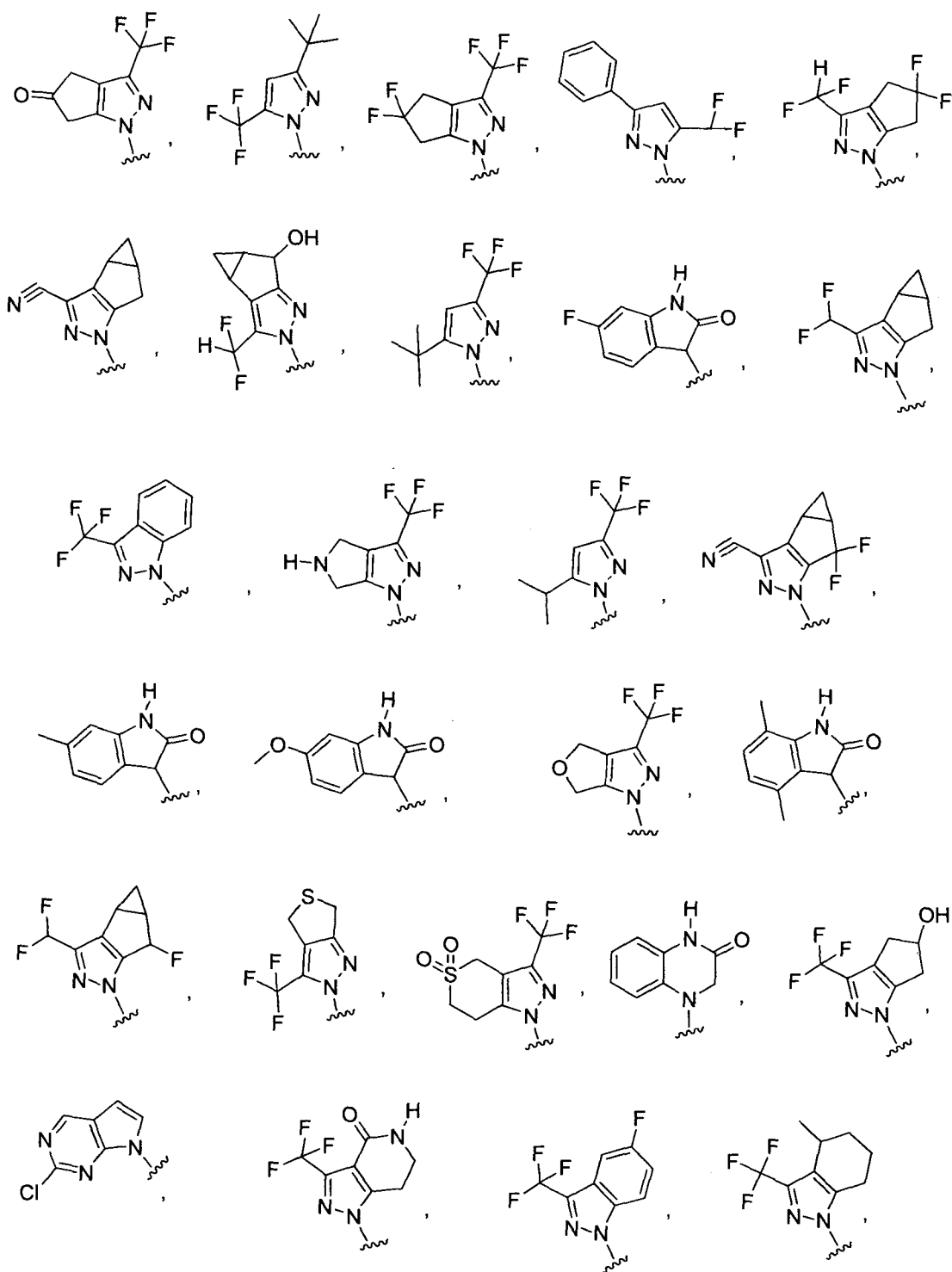
Another specific value for R^1 is:

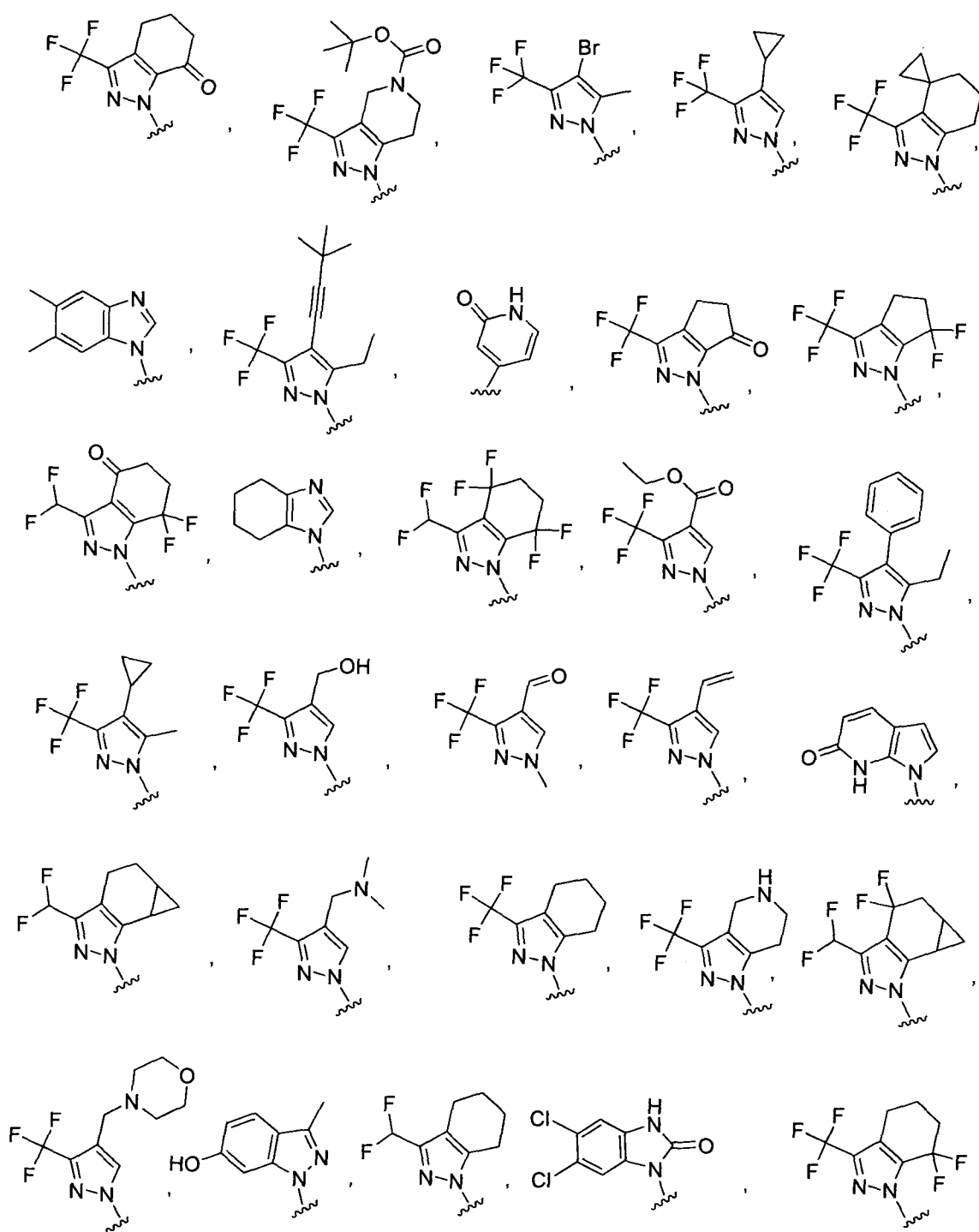


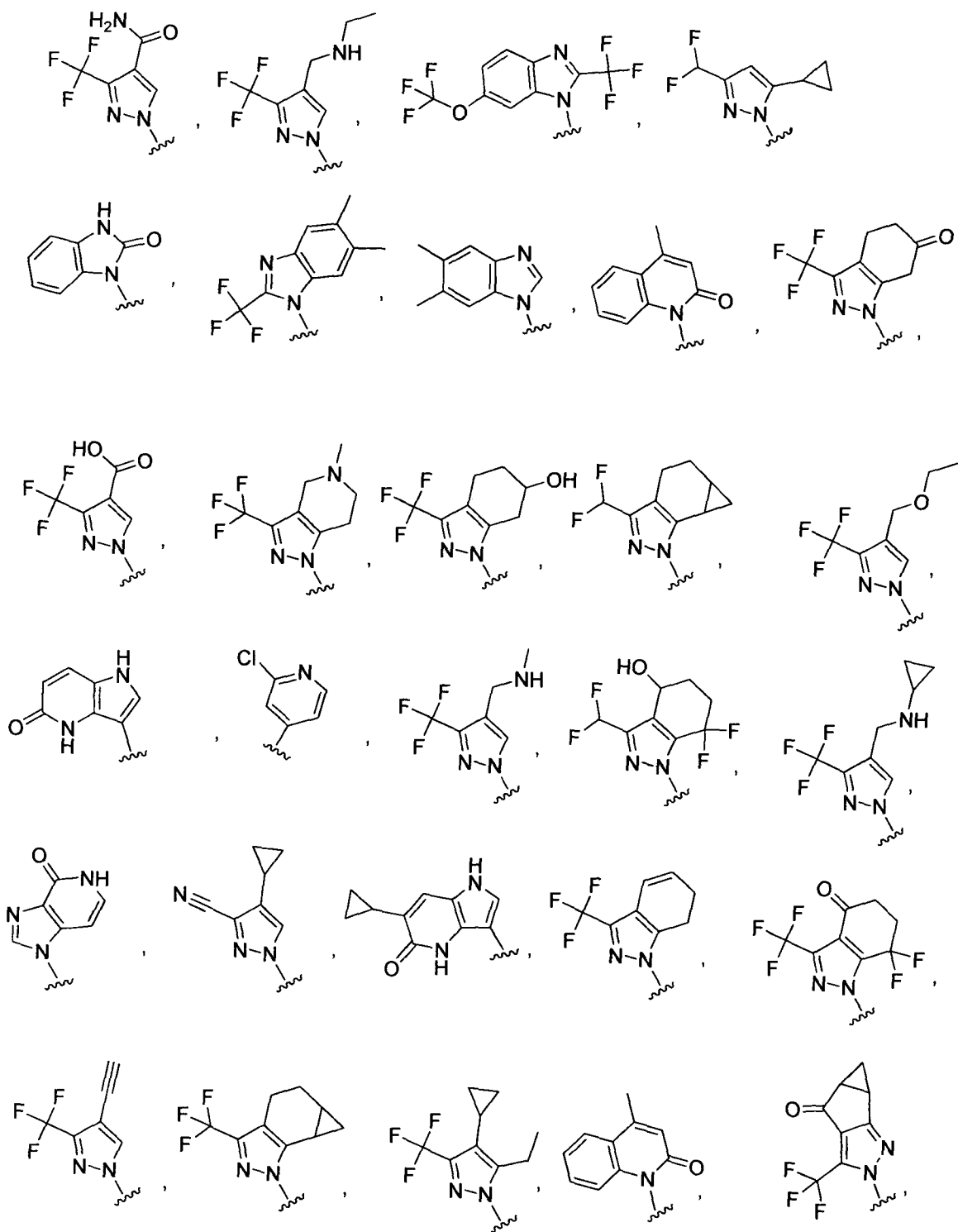


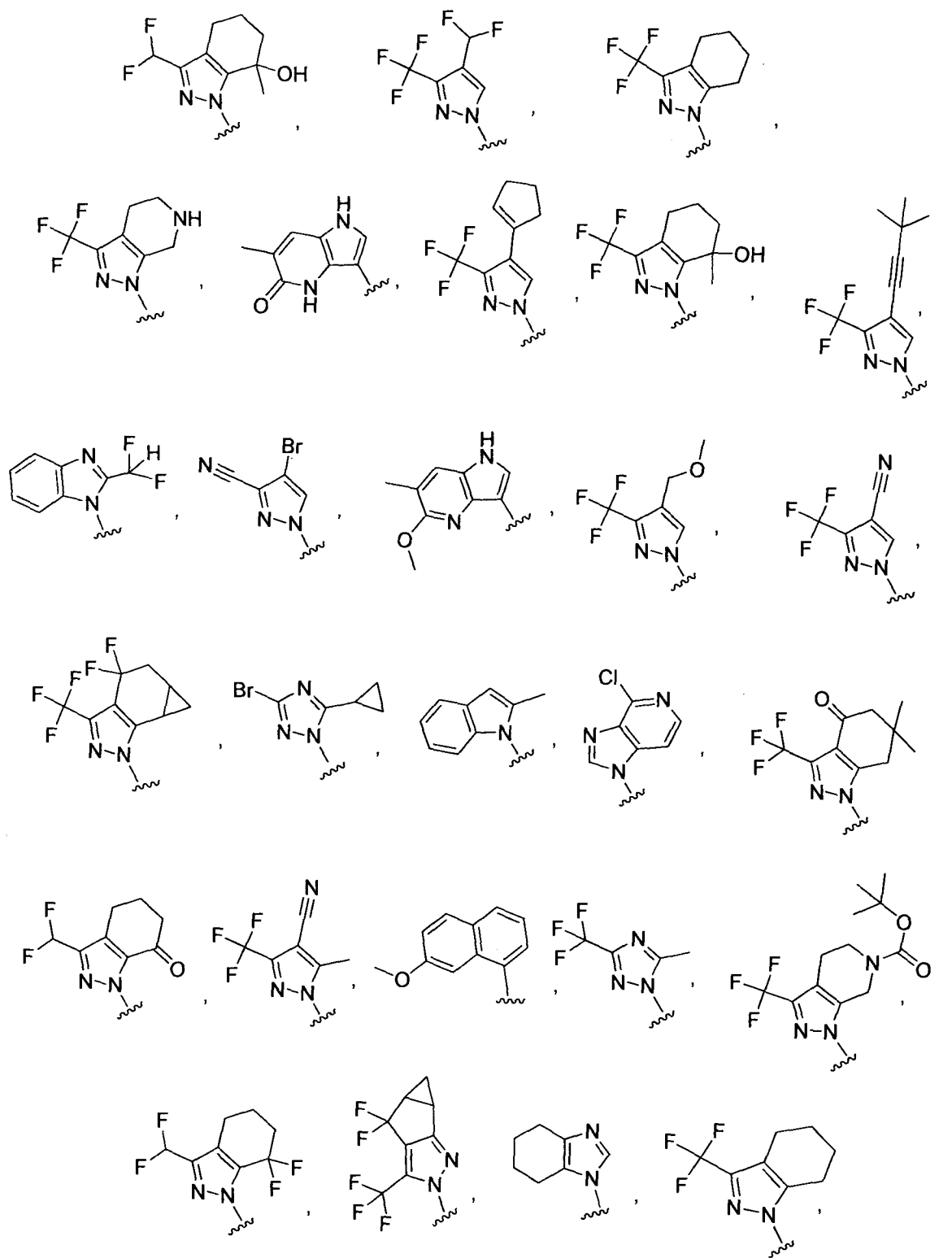


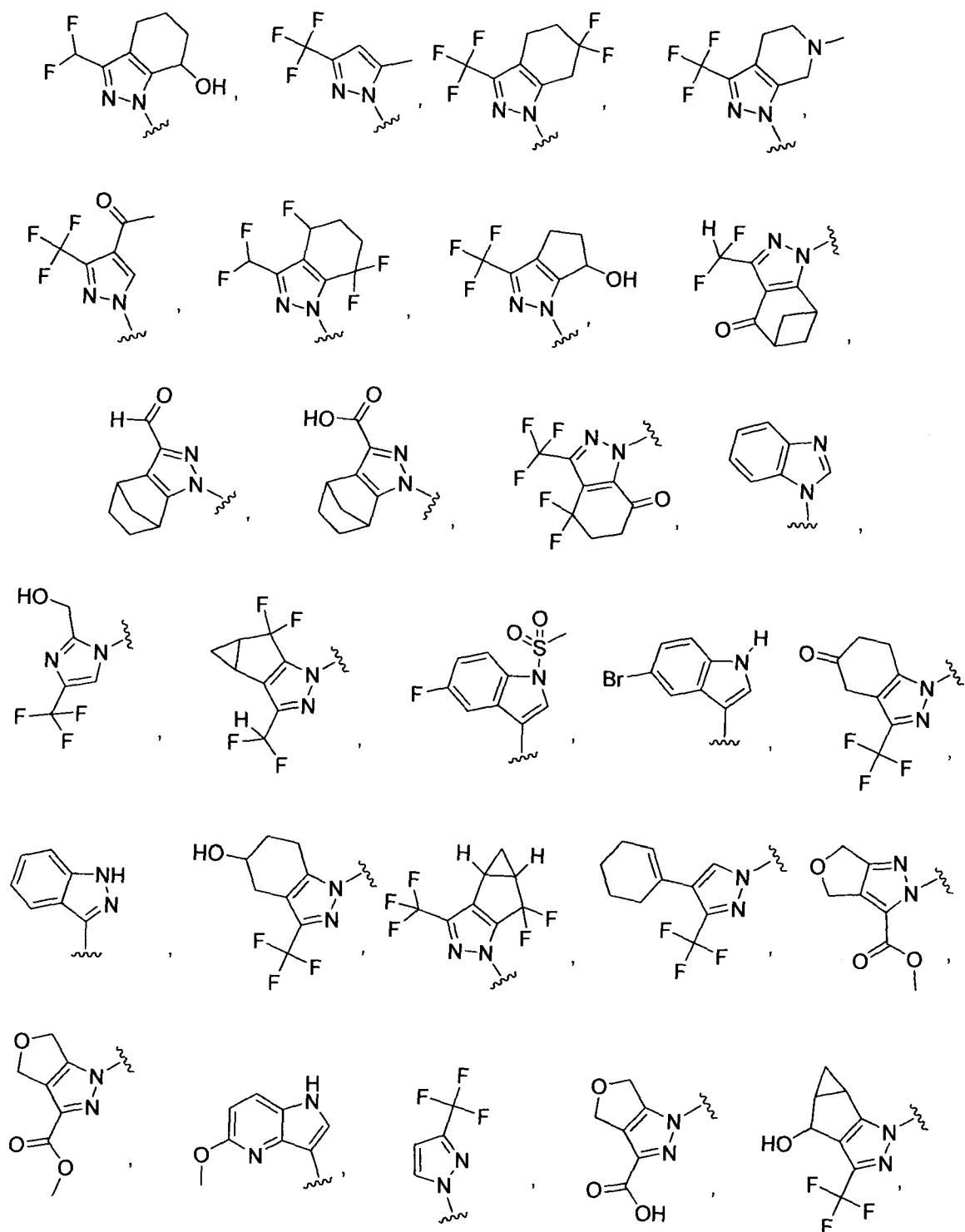


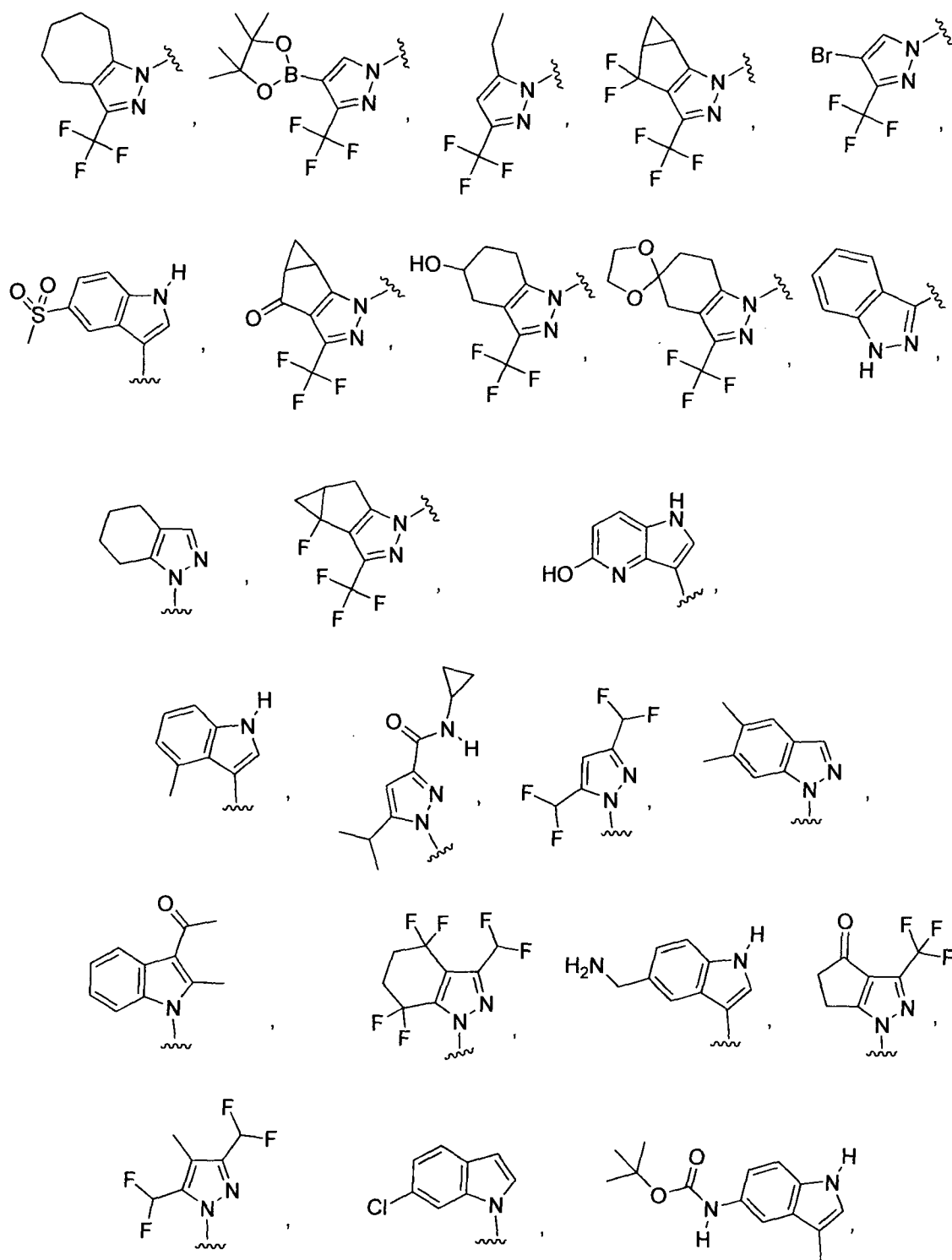


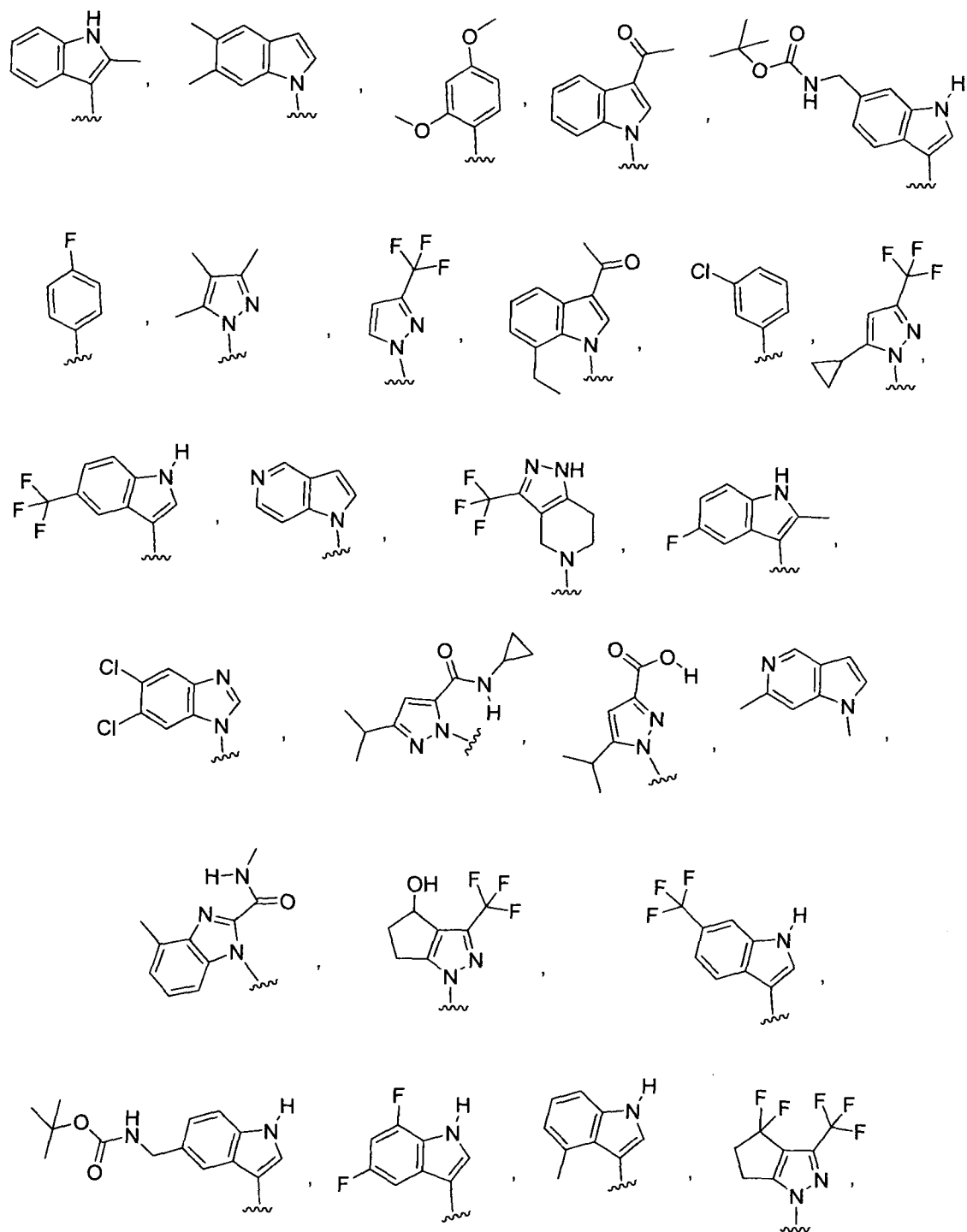


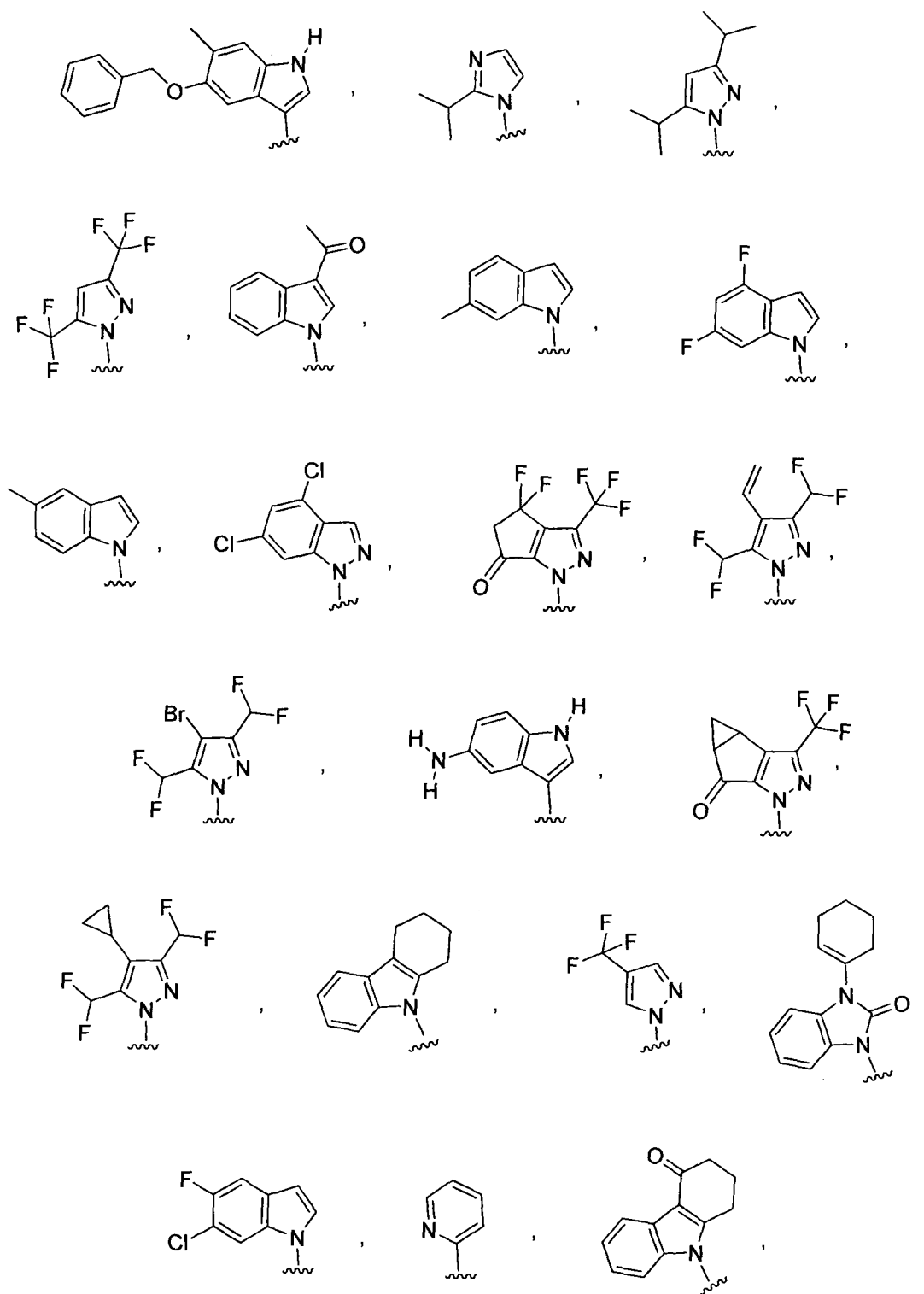


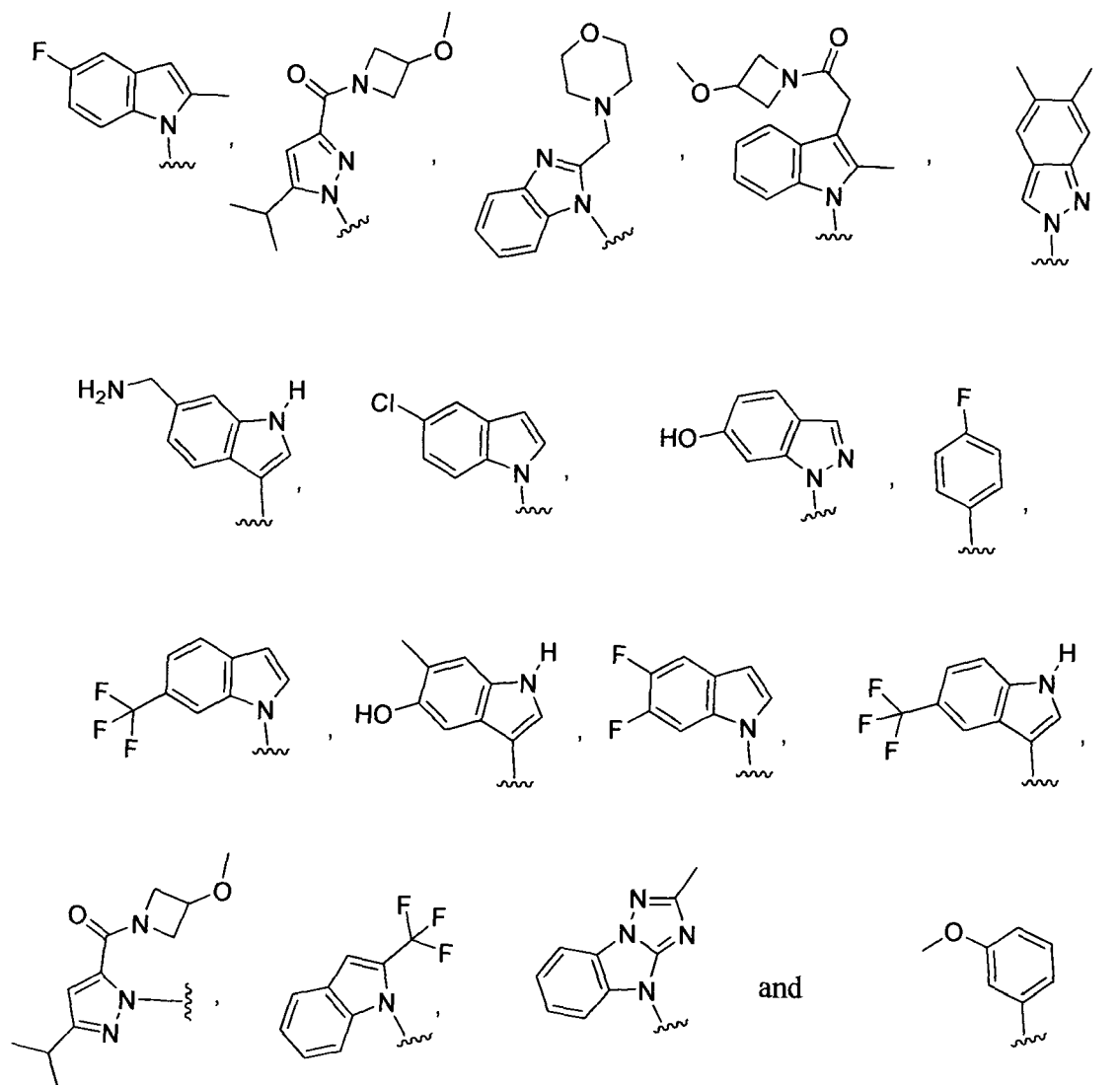




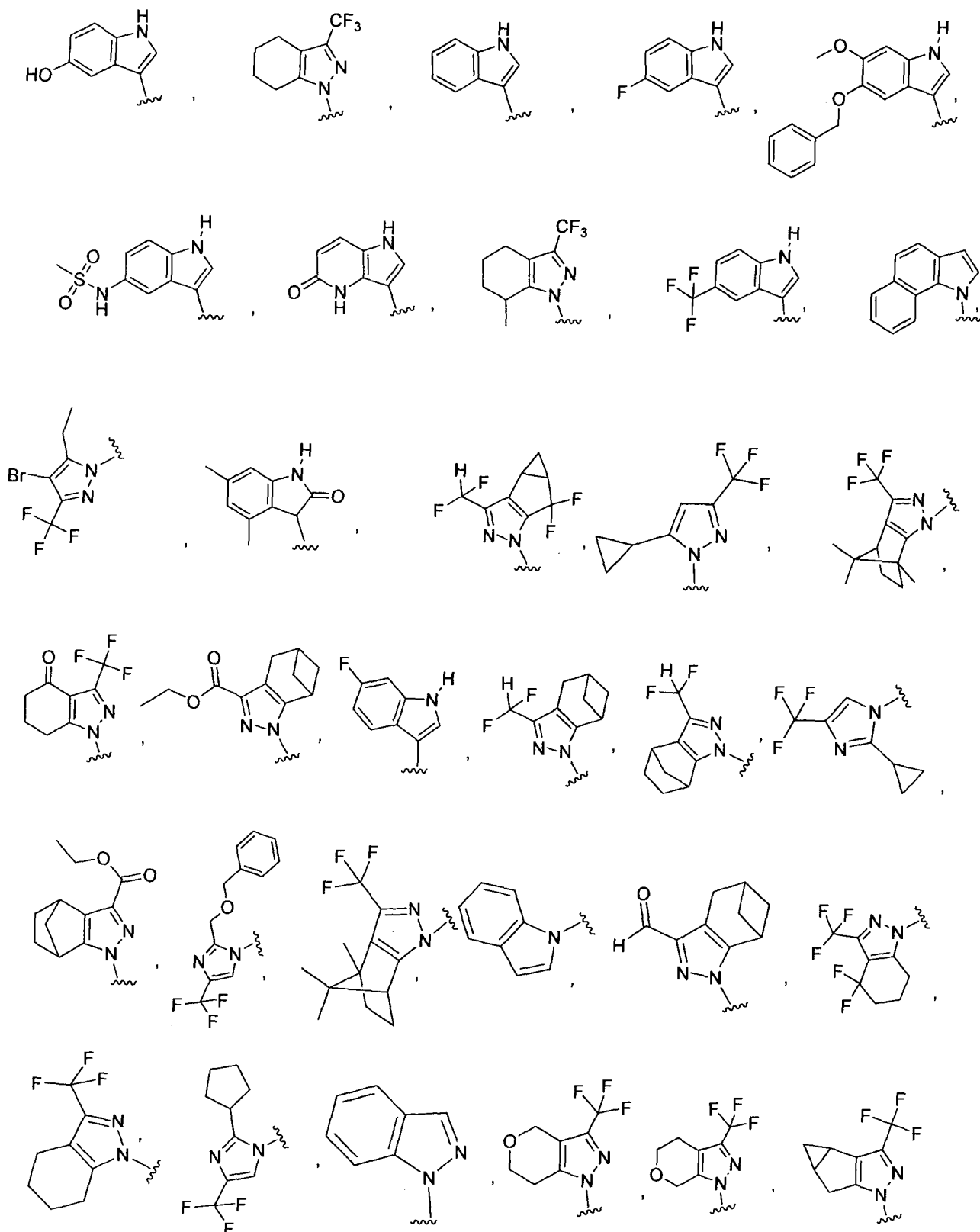


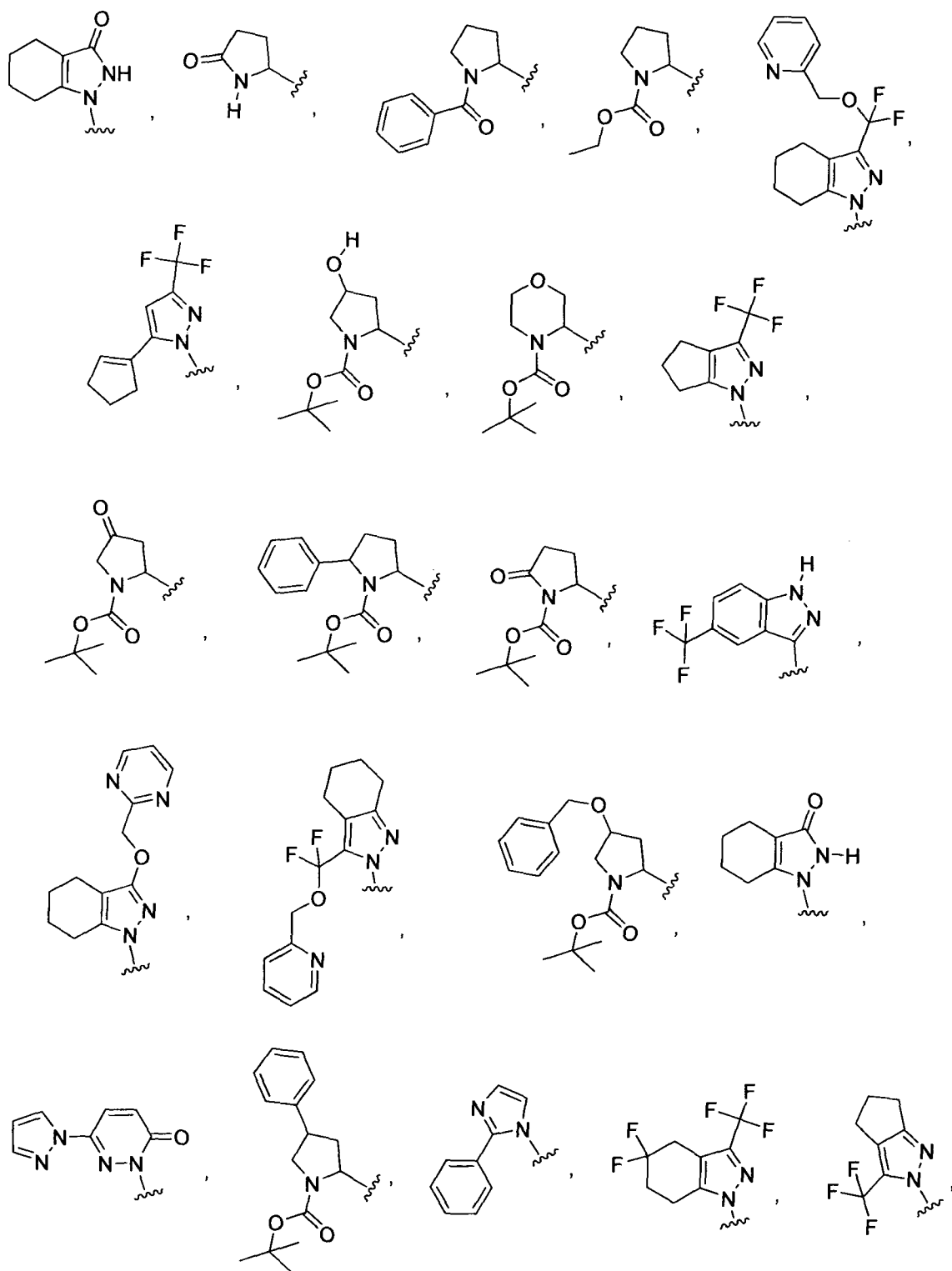


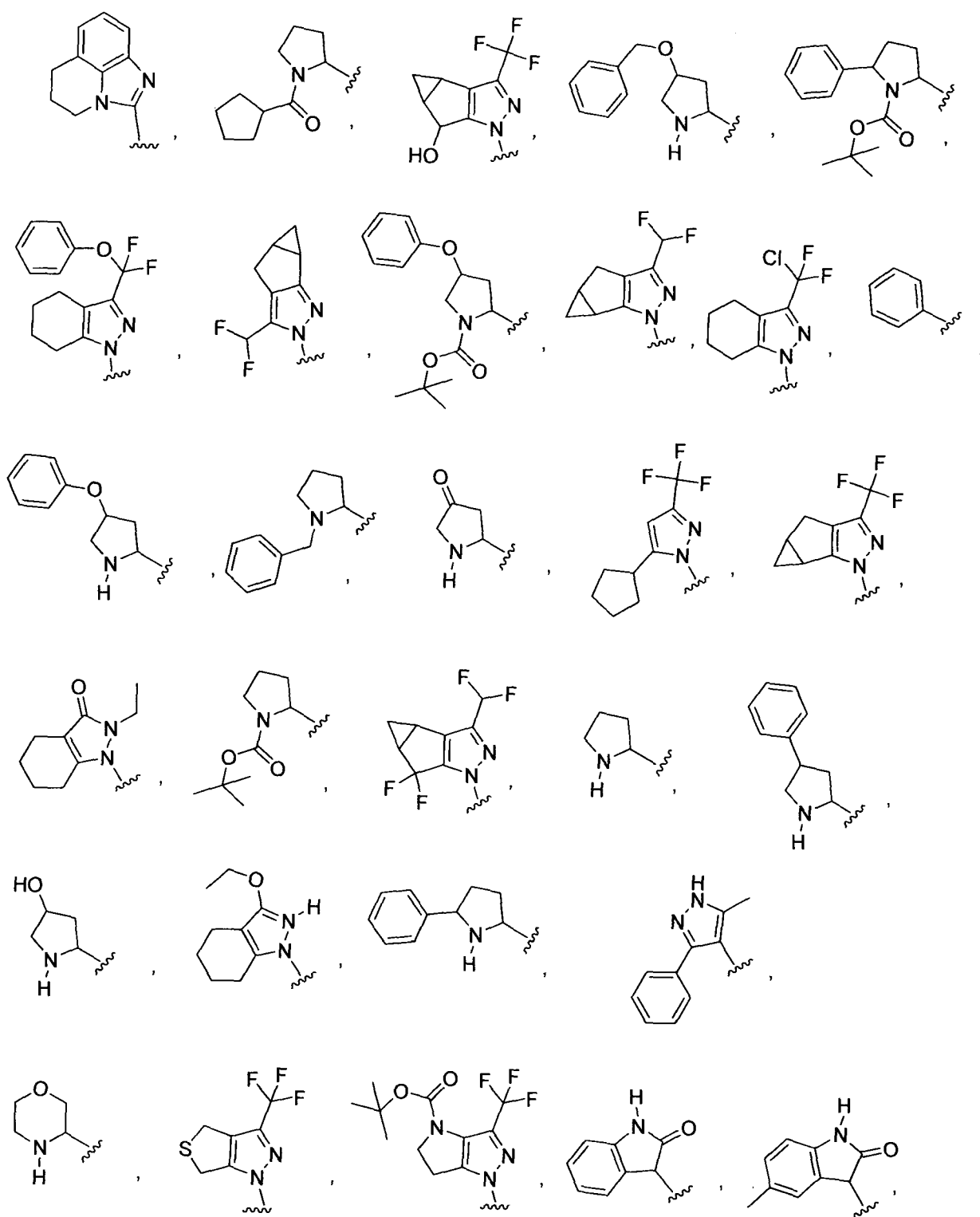


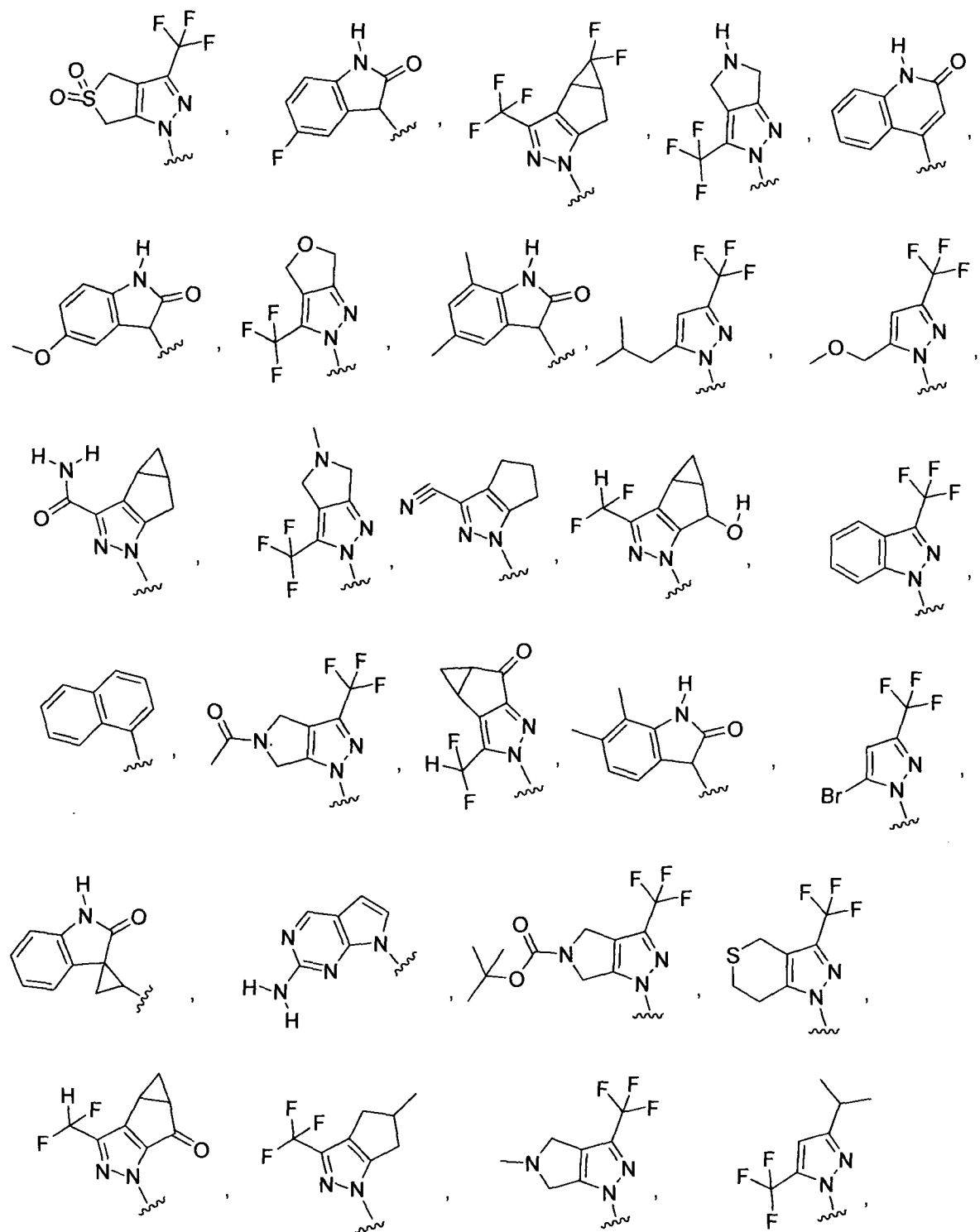


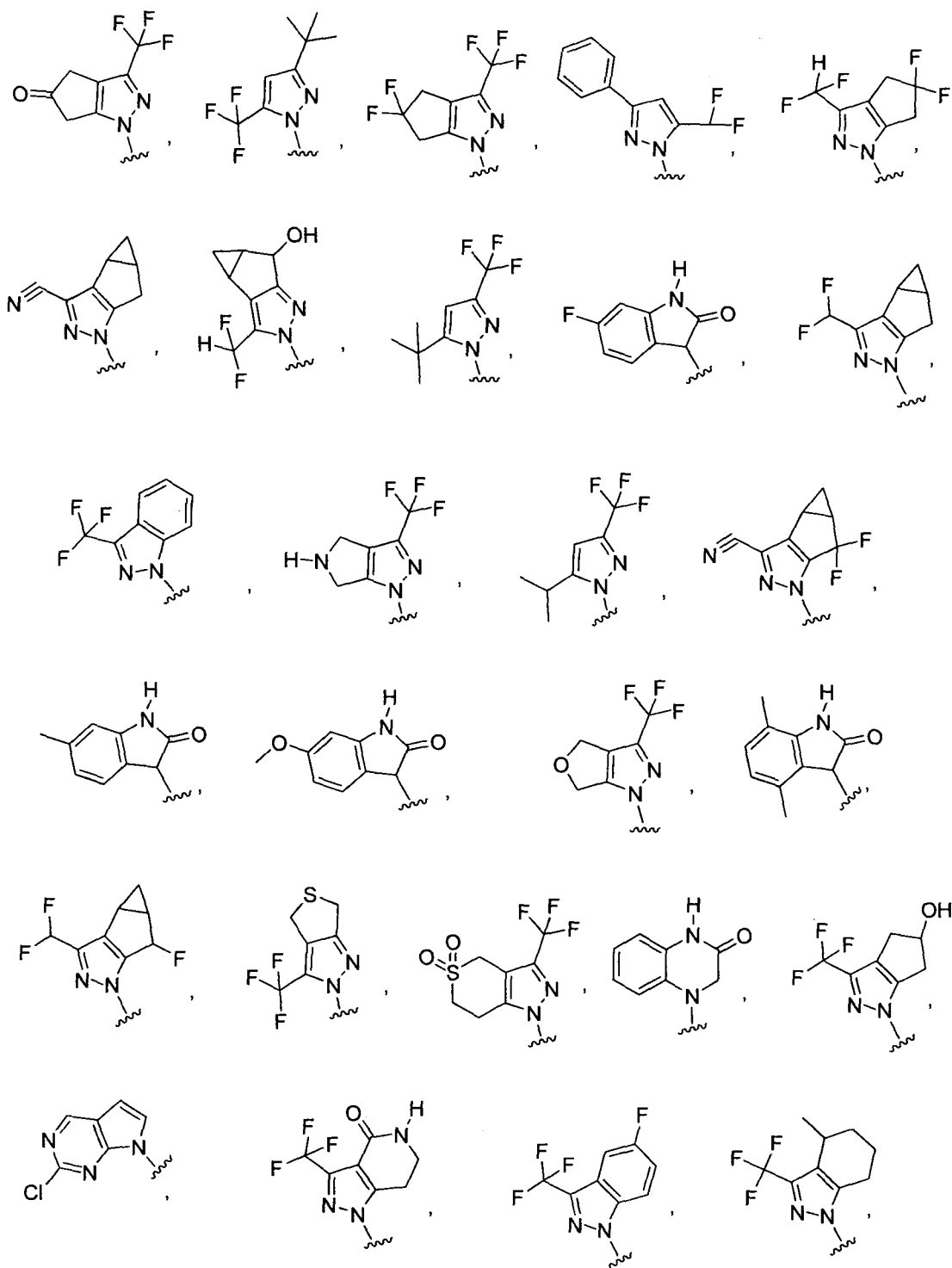
Another specific value for R^1 is:

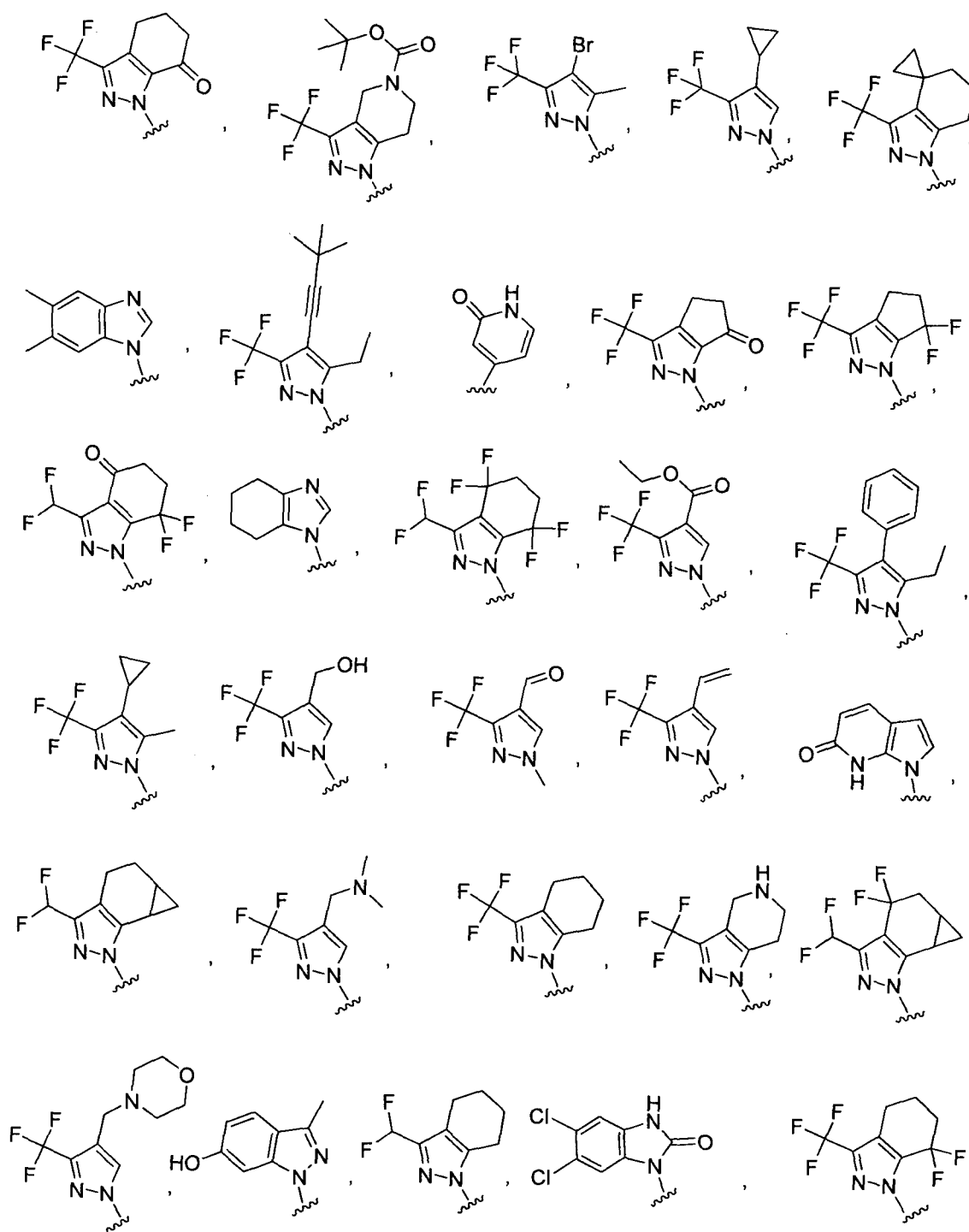


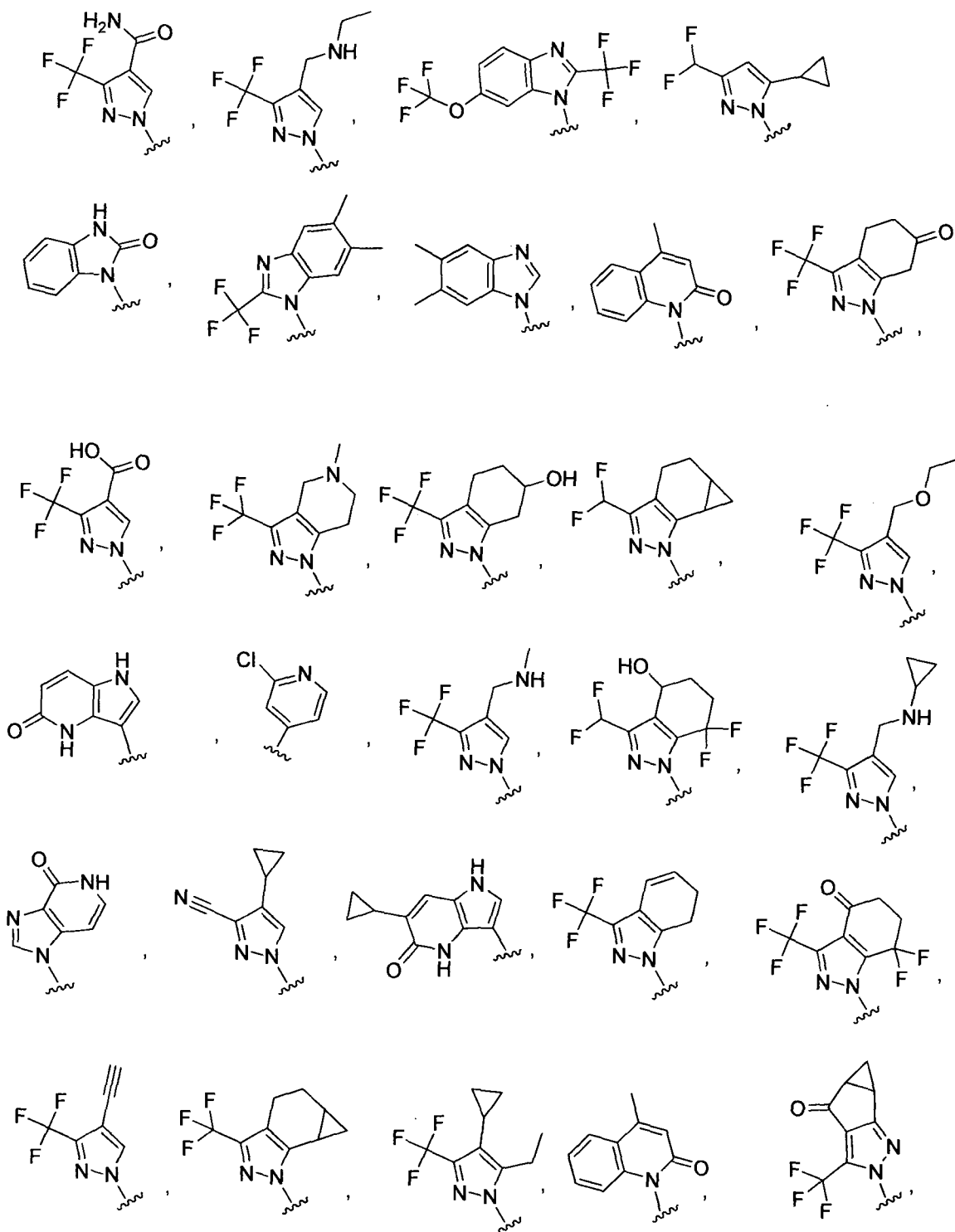


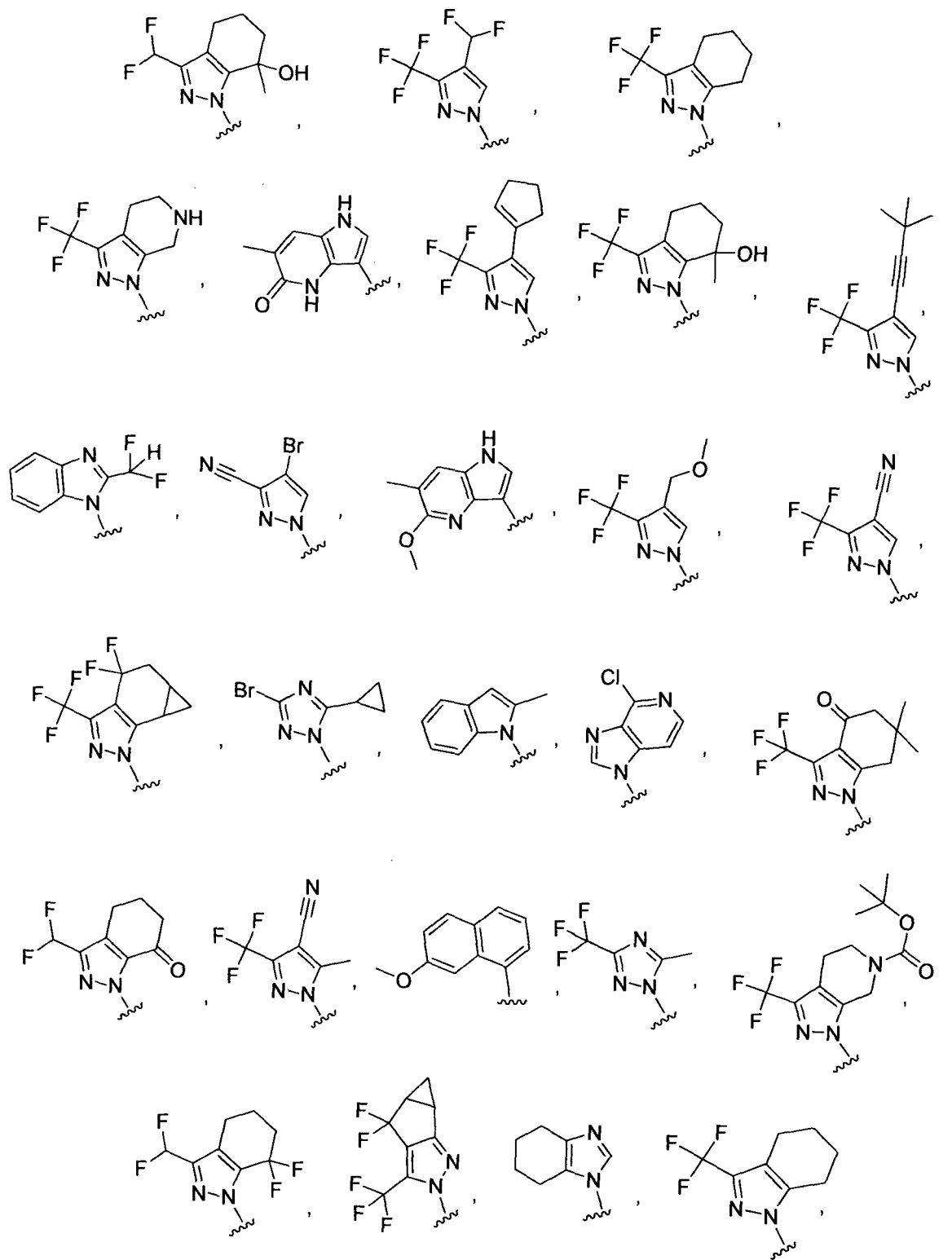


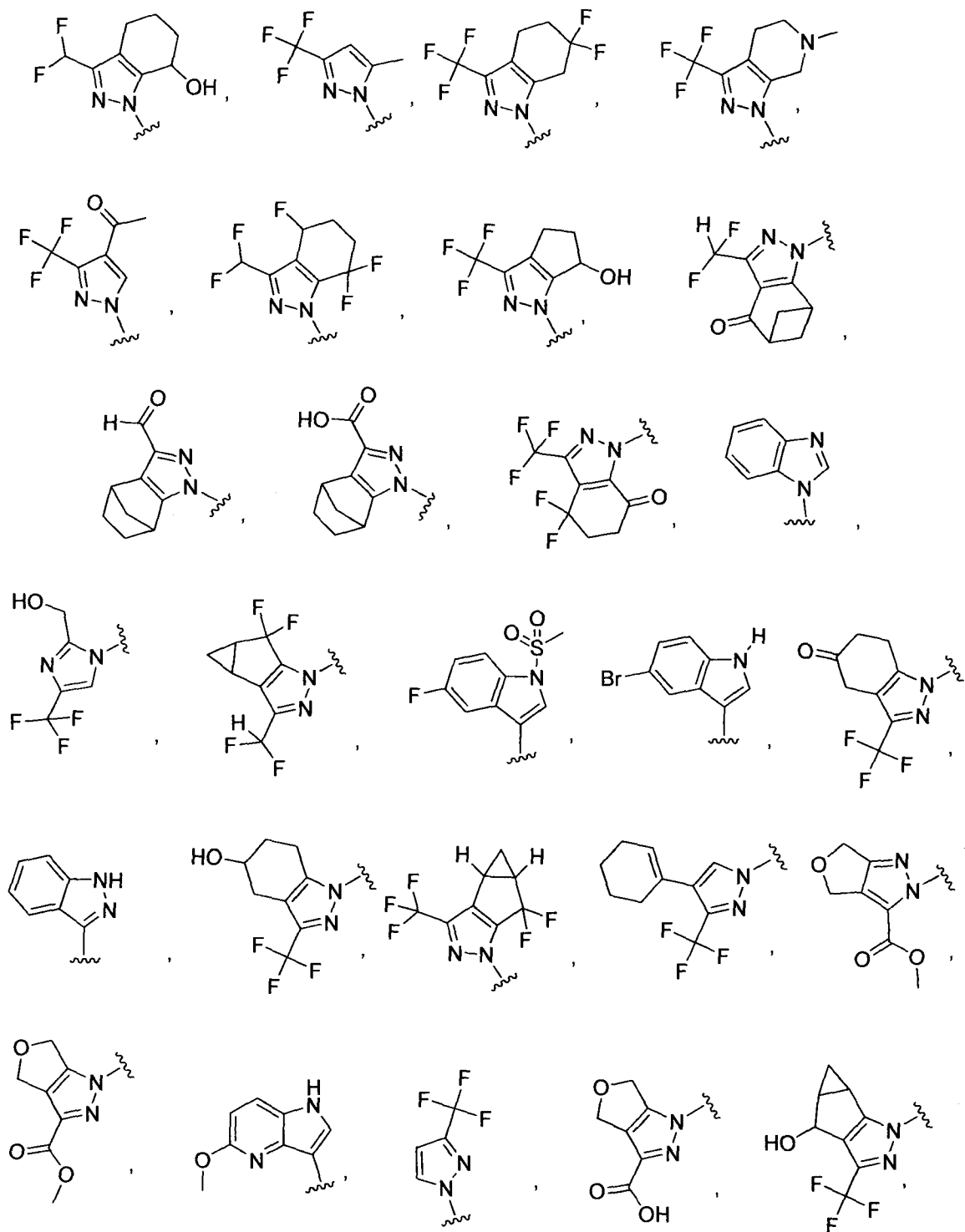


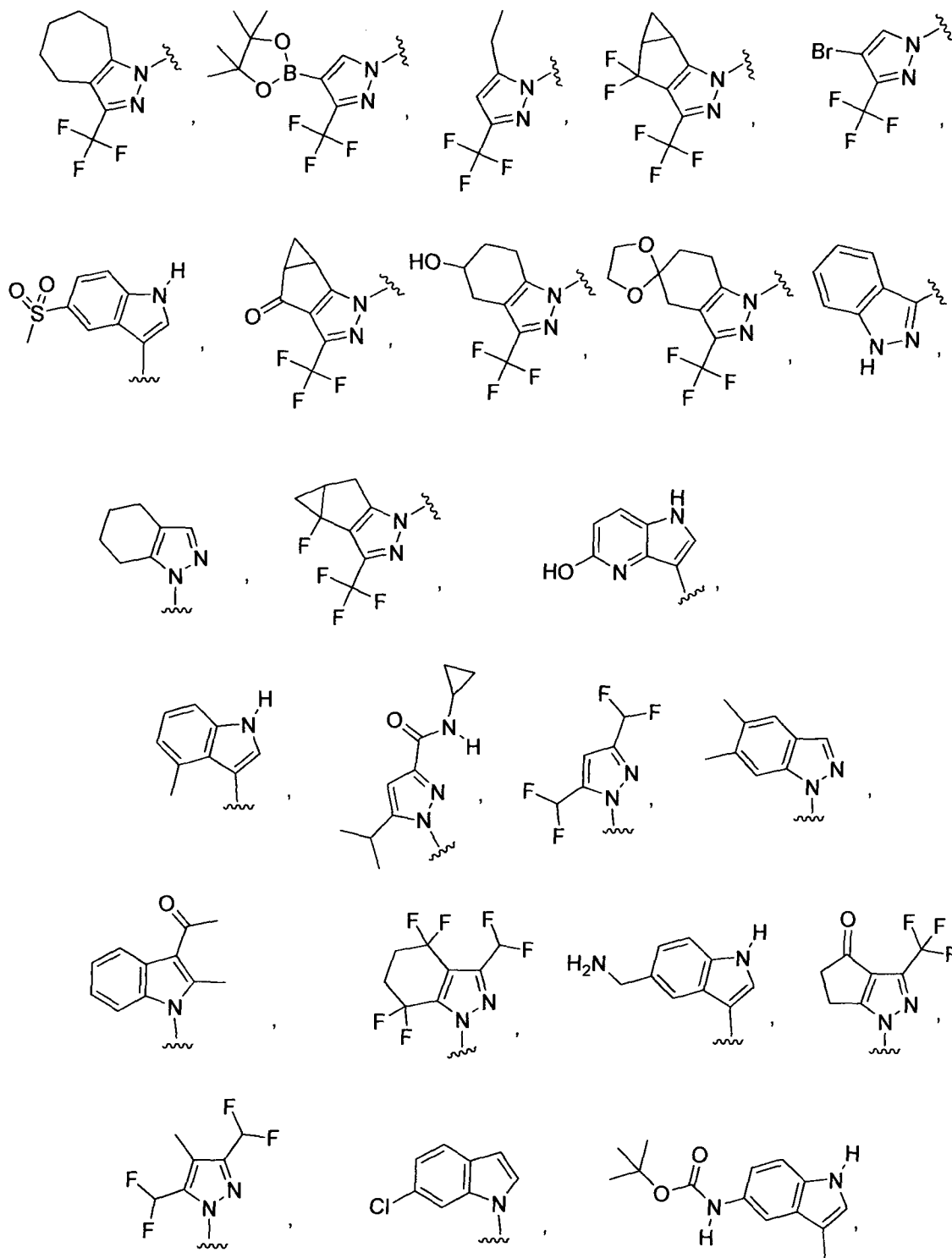


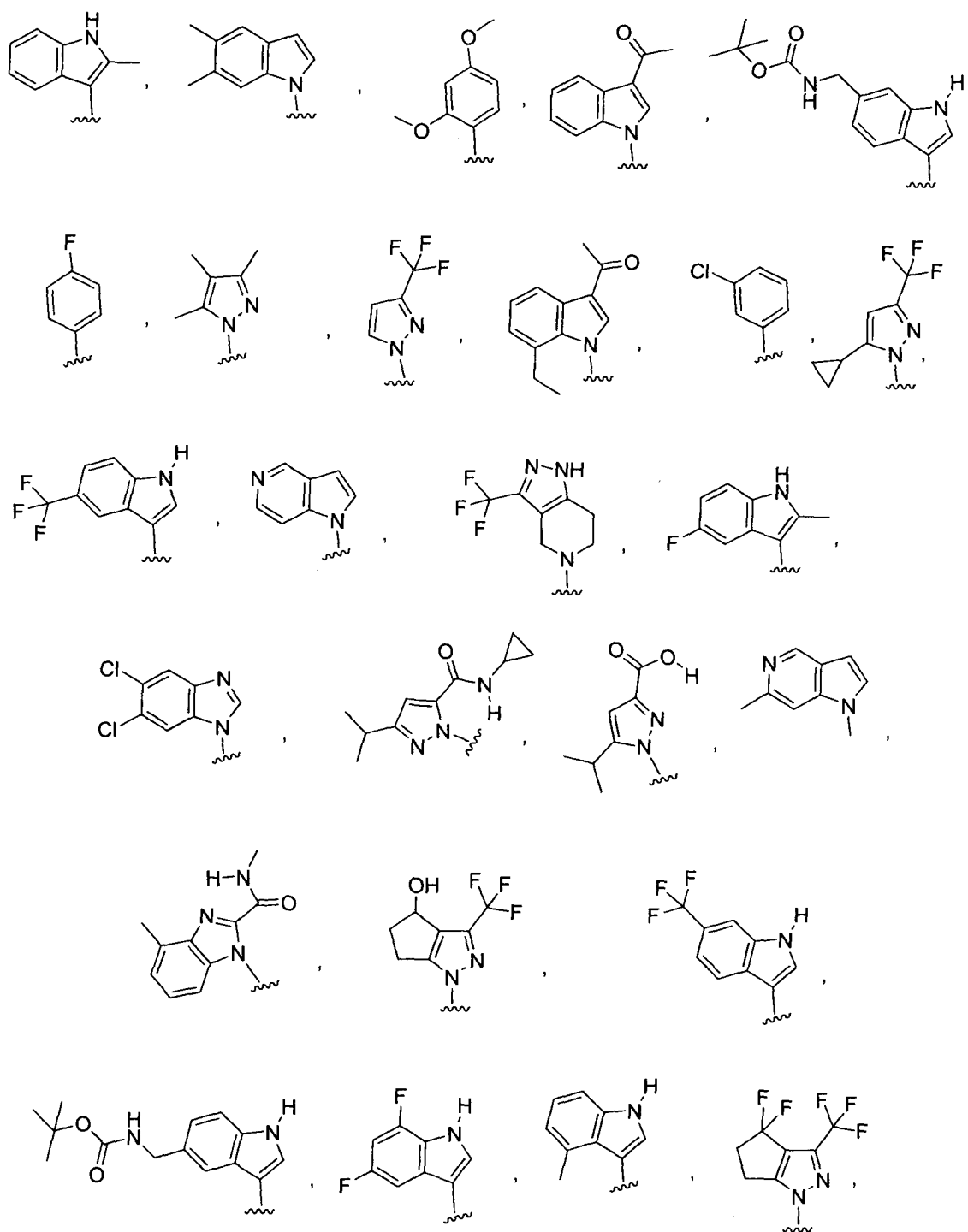


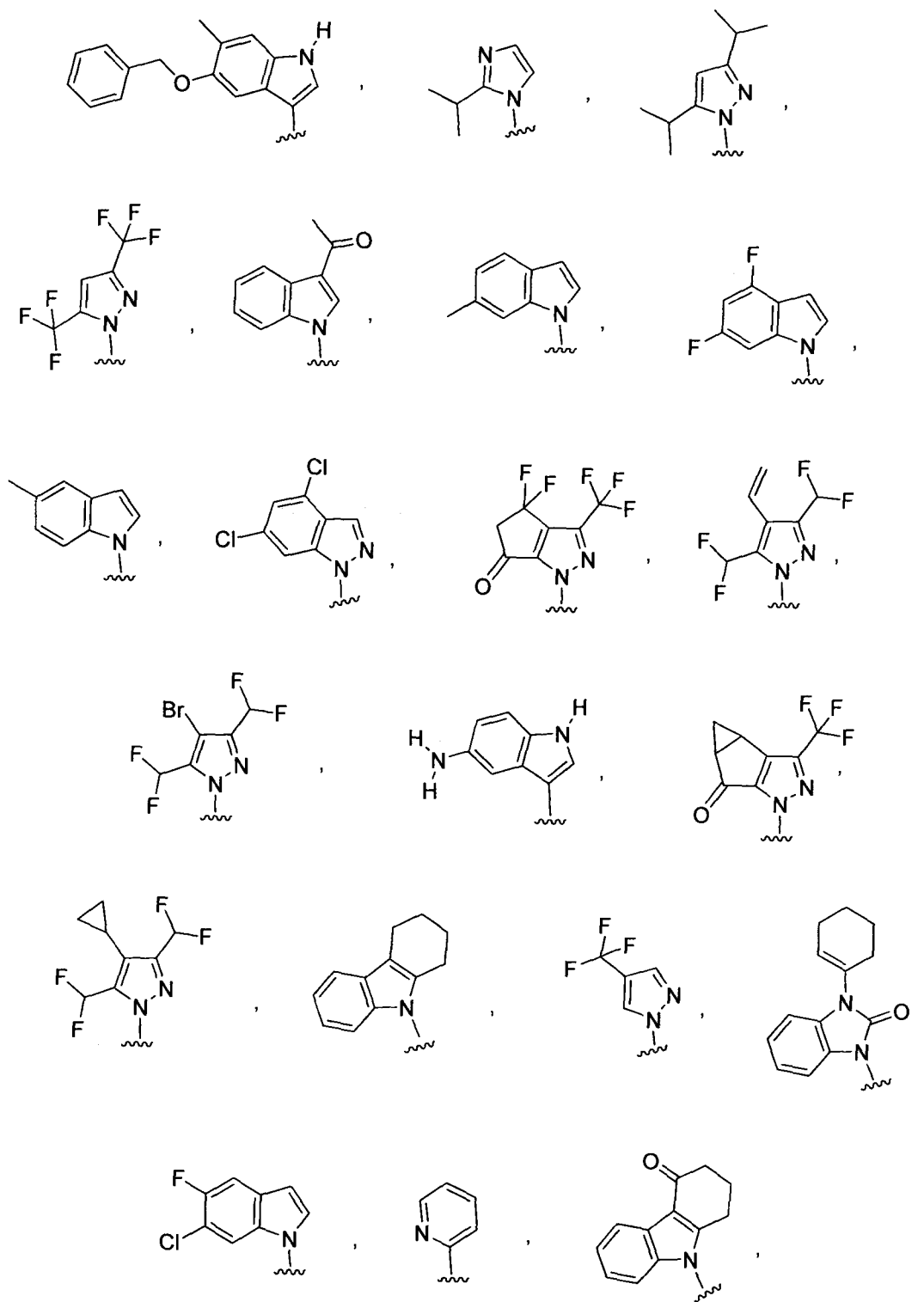


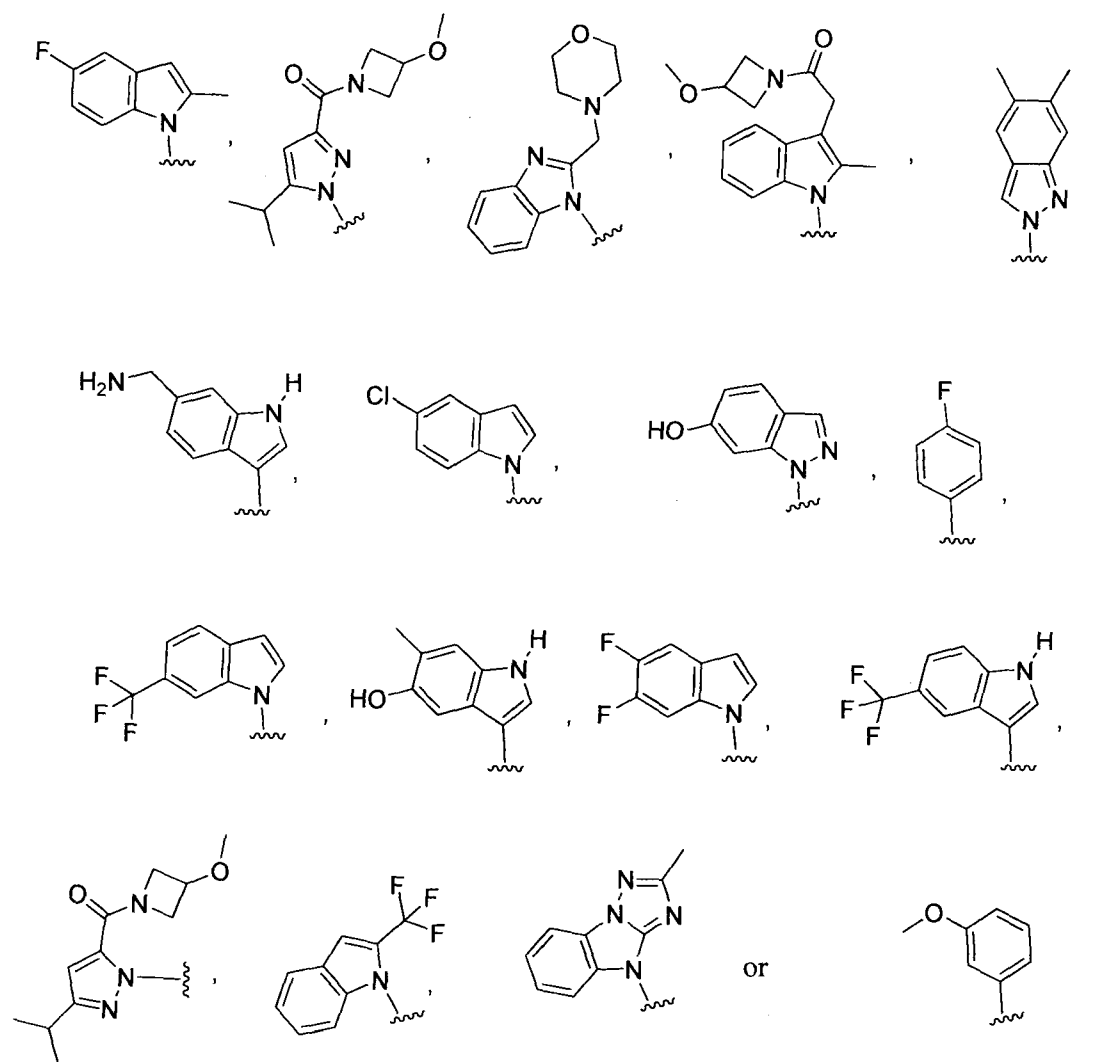






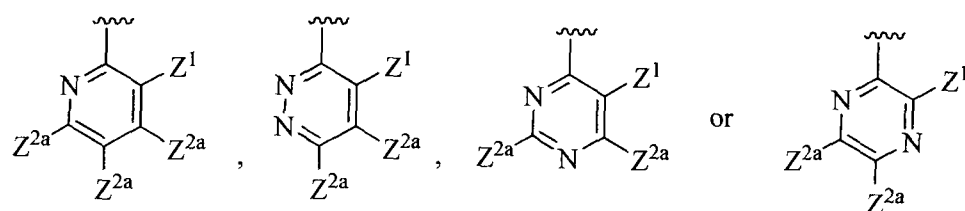






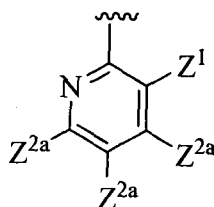
A specific value for A is pyridinyl, pyrimidinyl, pyrazinyl or pyridazinyl, wherein any pyridinyl, pyrimidinyl, pyrazinyl, or pyridazinyl of A is substituted with one Z^1 group and optionally substituted with one or more Z^2 groups.

Another specific value for A is:



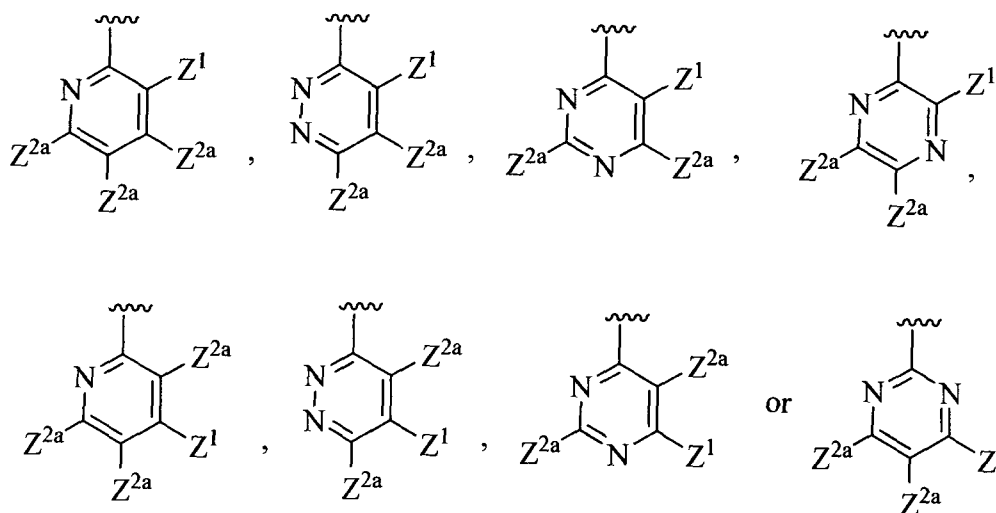
wherein each Z^{2a} is independently selected from H and Z^2 .

Another specific value for A is:



wherein each Z^{2a} is independently selected from H and Z^2 .

Another specific value for A is:



wherein each Z^{2a} is independently selected from H and Z^2 .

A specific value for Z^{2a} is H.

A specific value for Z^1 is (C_2-C_8) alkynyl, (C_3-C_7) carbocycle, aryl, heteroaryl or heterocycle, wherein any (C_3-C_7) carbocycle, aryl, heteroaryl or heterocycle of Z^1 is optionally substituted with one or more Z^{1a} or Z^{1b} groups and wherein any (C_2-C_8) alkynyl of Z^1 is optionally substituted with one or more Z^{1a} groups.

Another specific value for Z^1 is ethynyl, cyclohexyl, phenyl, pyridyl, thiophenyl, isoquinolinyl, 1,2,3,4-tetrahydroisoquinolinyl, indazolyl or isoindolin-1-one, wherein any cyclohexyl, phenyl, pyridyl, thiophenyl, isoquinolinyl, 1,2,3,4-tetrahydroisoquinolinyl, indazolyl or isoindolin-1-one of Z^1 is optionally substituted with one or more Z^{1a} or Z^{1b} groups, and wherein any ethynyl of Z^1 is optionally substituted with one or more Z^{1a} groups.

Another specific value for Z^1 is (C_2-C_8) alkynyl or aryl, wherein any aryl of Z^1 is optionally substituted with one or more Z^{1a} or Z^{1b} groups and wherein any (C_2-C_8) alkynyl of Z^1 is optionally substituted with one or more Z^{1a} groups.

Another specific value for Z^1 is ethynyl or phenyl, wherein any phenyl of Z^1 is optionally substituted with one or more Z^{1a} or Z^{1b} groups, and wherein any ethynyl of Z^1 is optionally substituted with one or more Z^{1a} groups.

Another specific value for Z^1 is (C_2-C_8) alkynyl, (C_3-C_7) carbocycle, aryl, heteroaryl or heterocycle, wherein any (C_3-C_7) carbocycle, aryl, heteroaryl, or heterocycle of Z^1 is optionally substituted with one or more Z^{1a} or Z^{1b} groups and wherein any (C_2-C_8) alkynyl of Z^1 is optionally substituted with one or more Z^{1a} groups.

Another specific value for Z^1 is (C_2-C_8) alkynyl, aryl, heteroaryl or heterocycle, wherein any aryl, heteroaryl, or heterocycle of Z^1 is optionally substituted with one or more Z^{1a} or Z^{1b} groups and wherein any (C_2-C_8) alkynyl of Z^1 is optionally substituted with one or more Z^{1a} groups.

Another specific value for Z^1 is aryl, heteroaryl or heterocycle, wherein any aryl, heteroaryl, or heterocycle of Z^1 is optionally substituted with one or more Z^{1a} or Z^{1b} groups.

A specific value for Z^{1a} is (C_3-C_7) carbocycle, heteroaryl, heterocycle, halogen, -CN, -OR_{n2}, -S(O)₂NR_{q2}R_{r2}, -NR_{q2}R_{r2}, -C(O)R_{n2}, -C(O)NR_{p2}R_{q2} or -C(=NOR_{n2})CN, wherein any (C_3-C_7) carbocycle, heteroaryl or heterocycle of Z^{1a} is optionally substituted with one or more Z^{1c} or Z^{1d} groups, and each Z^{1b} is independently selected from (C_1-C_8) alkyl, wherein any (C_1-C_8) alkyl of Z^{1b} is optionally substituted with one or more Z^{1c} groups.

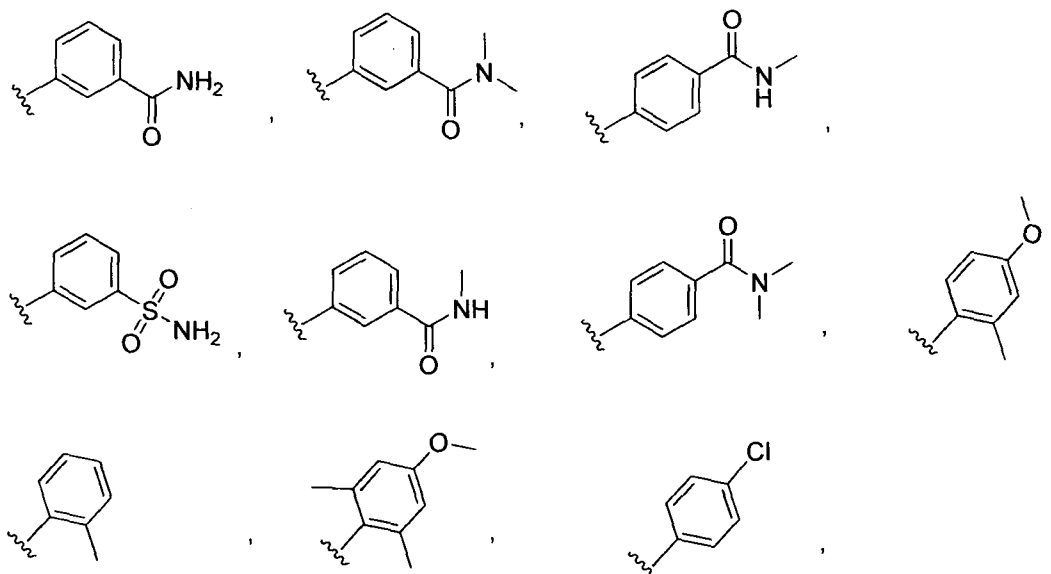
Another specific value for Z^{1a} is cyclopropyl, N-ethyl-3-amine-oxetan-3-yl, N-ethyl-1-amine-2,2,2-trifluoroethyl, triazol-1-yl, tetrazol-5-yl, 3-trifluoromethylisoxazol-5-yl, 2-carboxy-ethyl, 2-morpholinoethoxy, fluoro, chloro, -CN, methoxy, -S(O)₂NH₂, -C(=NOCH₃)CN, -C(O)NH₂, -C(O)N(CH₃)₂ or -C(O)NH(CH₃), and wherein each Z^{1b} is methyl.

Another specific value for Z^{1a} is aryl, heteroaryl, heterocycle, (C_3-C_7) carbocycle, halogen, CN, -OR_{n2}, -S(O)₂R_{p2}, -S(O)₂NR_{q2}R_{r2}, -NR_{q2}R_{r2}, -NR_{n2}COR_{p2}, -NR_{n2}CO₂R_{p2}, -NR_{n2}CONR_{q2}R_{r2}, -NR_{n2}S(O)₂R_{p2}, -C(O)R_{n2} and -C(O)NR_{q2}R_{r2}, wherein any aryl, heteroaryl, heterocycle and (C_3-C_7) carbocycle of Z^{1a} is optionally substituted with one or more (e.g. 1, 2, 3, 4 or 5) Z^{1c} or Z^{1d} groups; and each Z^{1b} is independently selected from (C_1-C_8) alkyl and (C_2-C_8) alkynyl, wherein any (C_1-C_8) alkyl 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.

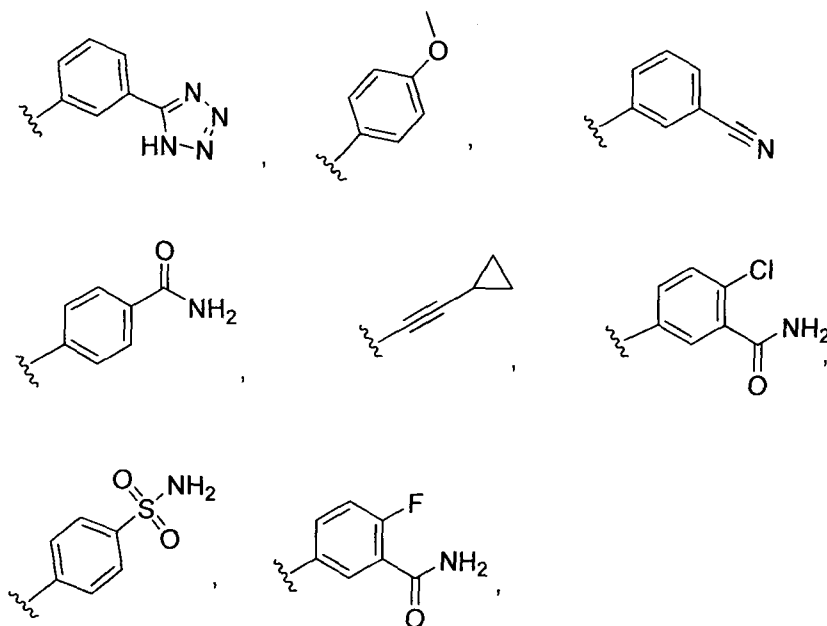
Another specific value for Z^{1a} is aryl, heteroaryl, heterocycle, halogen, CN, -OR_{n2}, -S(O)₂R_{p2}, -S(O)₂NR_{q2}R_{r2}, -NR_{q2}R_{r2}, -NR_{n2}COR_{p2}, -NR_{n2}CO₂R_{p2}, -NR_{n2}CONR_{q2}R_{r2}, -NR_{n2}S(O)₂R_{p2}, -C(O)R_{n2} and -C(O)NR_{q2}R_{r2}, wherein any aryl, heteroaryl, heterocycle and (C_3-C_7) carbocycle of Z^{1a} is optionally substituted with one or more (e.g. 1, 2, 3, 4 or 5) Z^{1c} or Z^{1d}

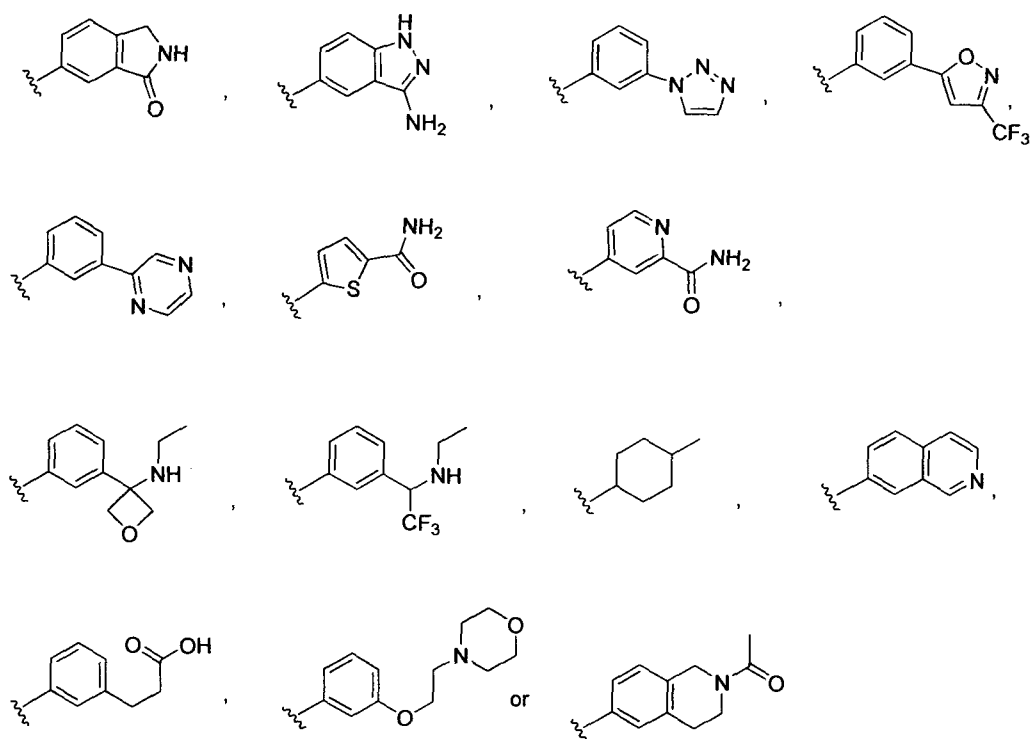
groups; and each Z^{1b} is independently selected from (C_1-C_8) alkyl and (C_2-C_8) alkynyl, wherein any (C_1-C_8) alkyl and (C_2-C_8) alkynyl of Z^{1b} is optionally substituted with one or more (e.g. 1, 2, 3, 4 or 5) Z^{1c} groups.

A specific value for Z^1 is:

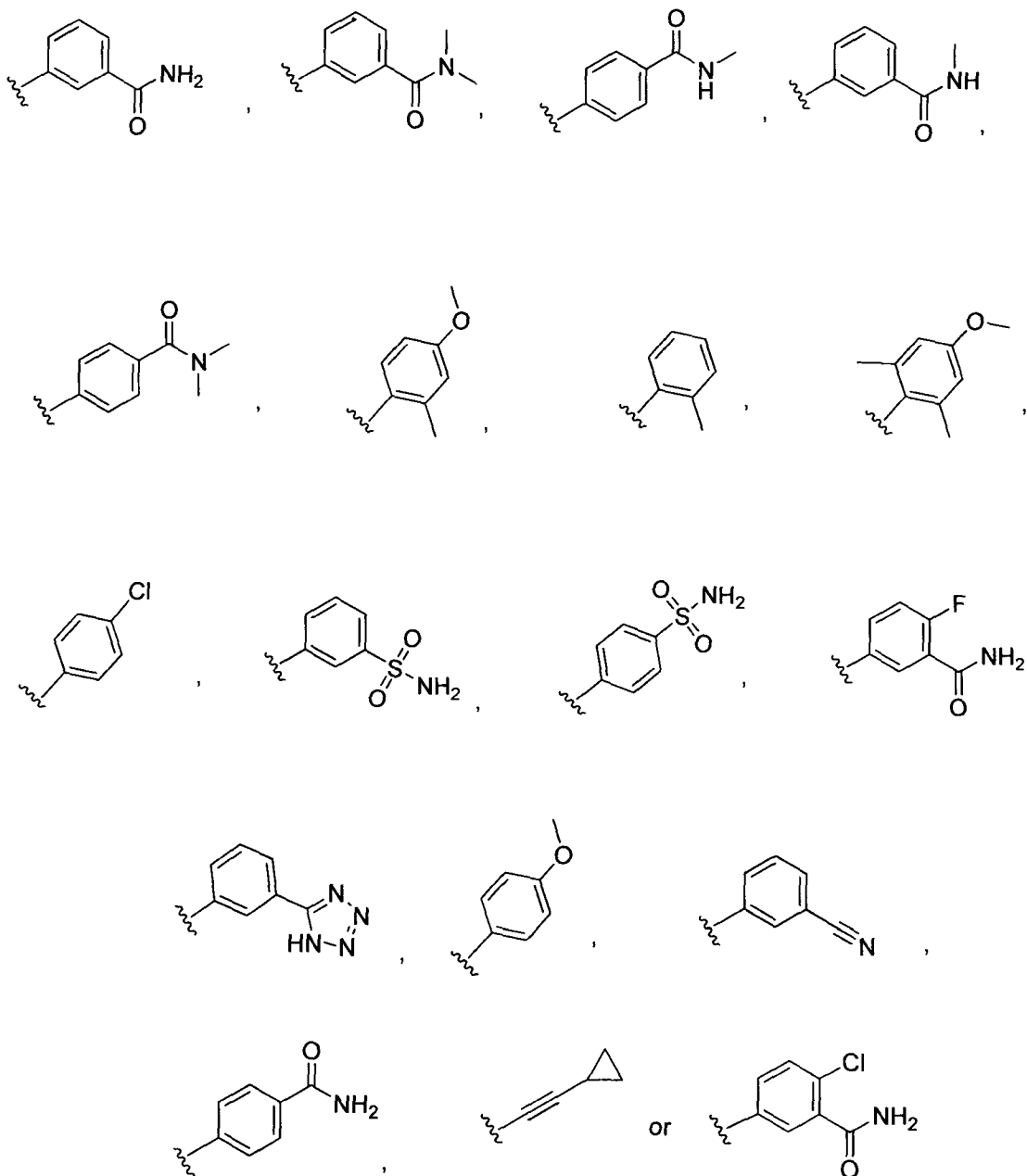


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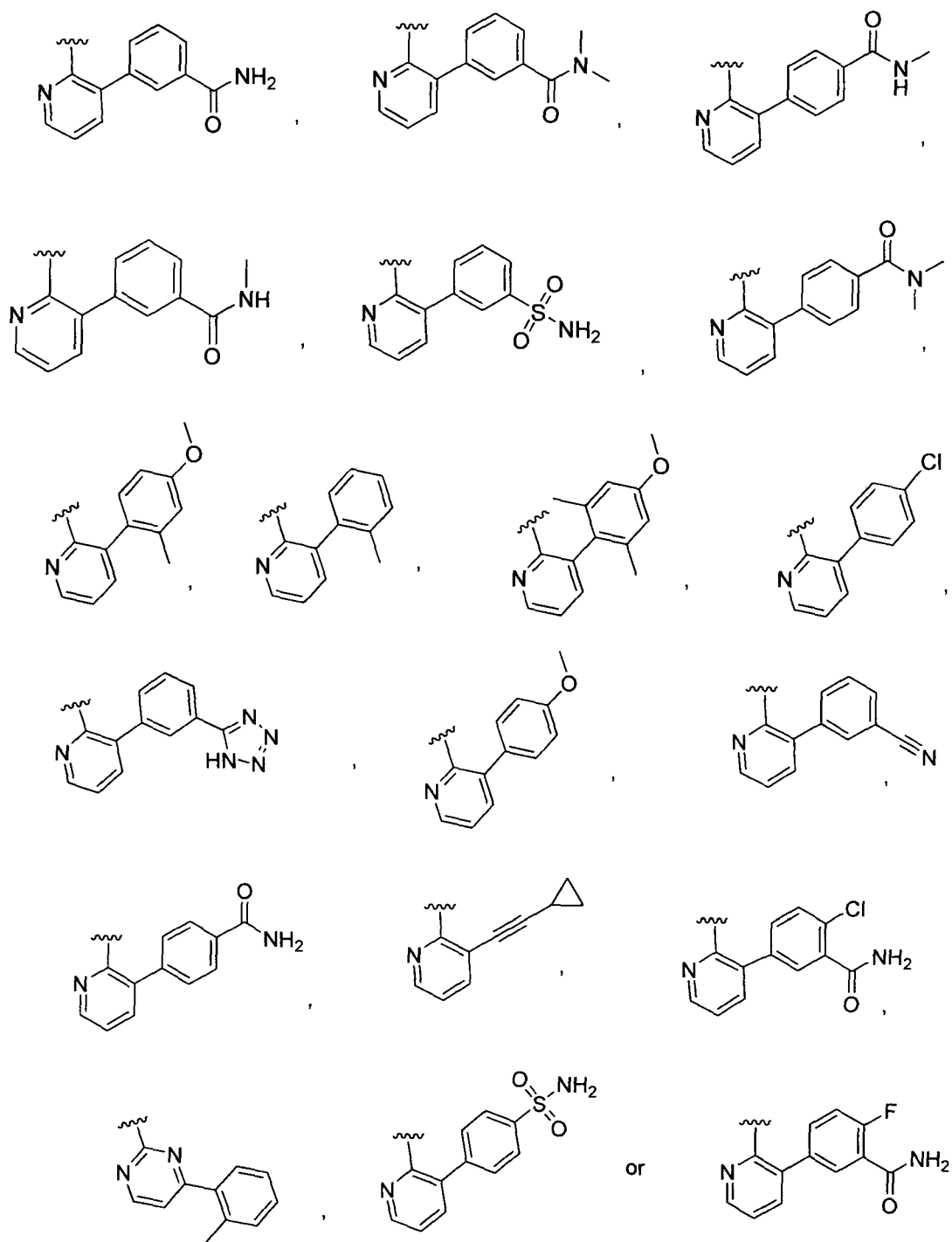


Another value for Z^1 is:

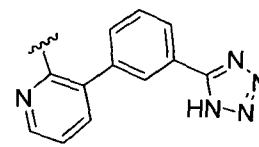
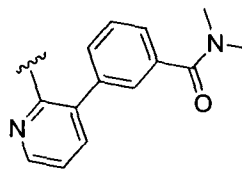
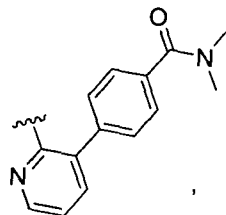
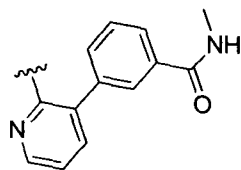
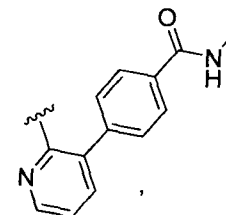
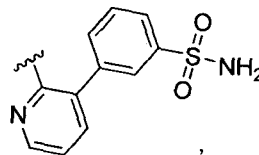
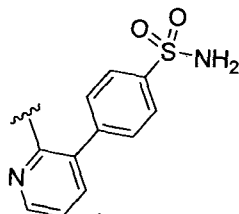
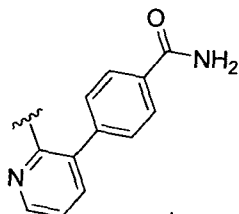
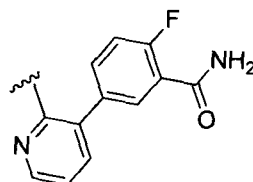
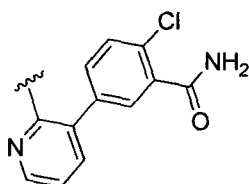
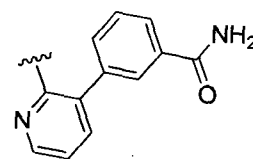
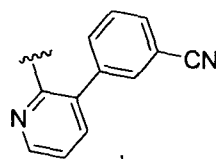
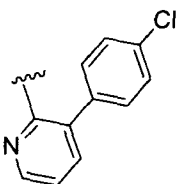
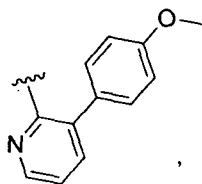
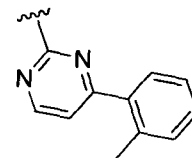
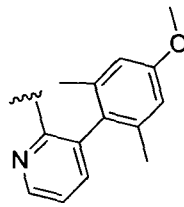
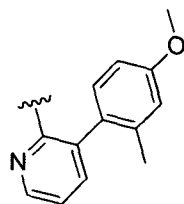
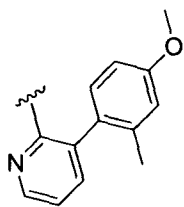


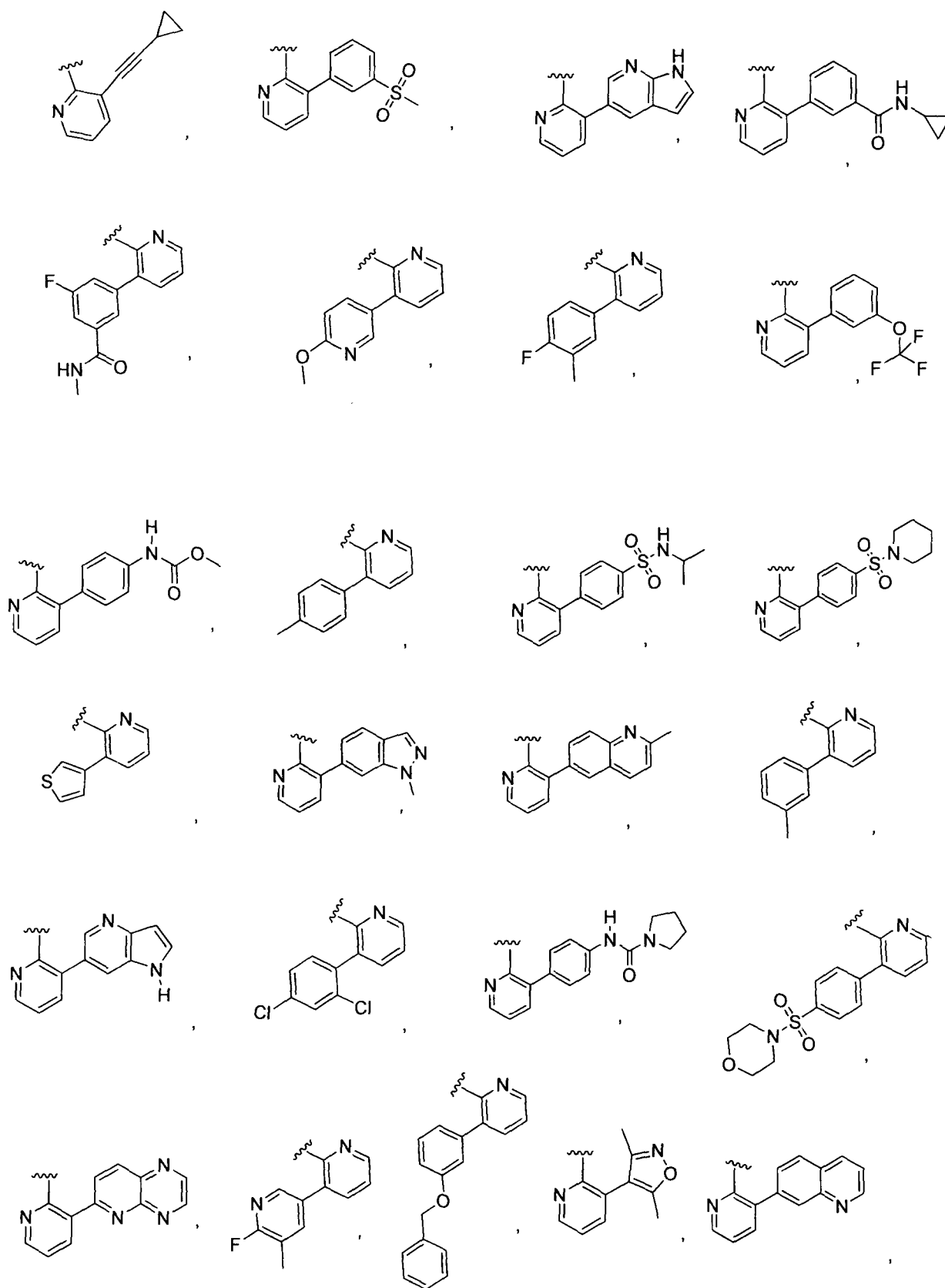
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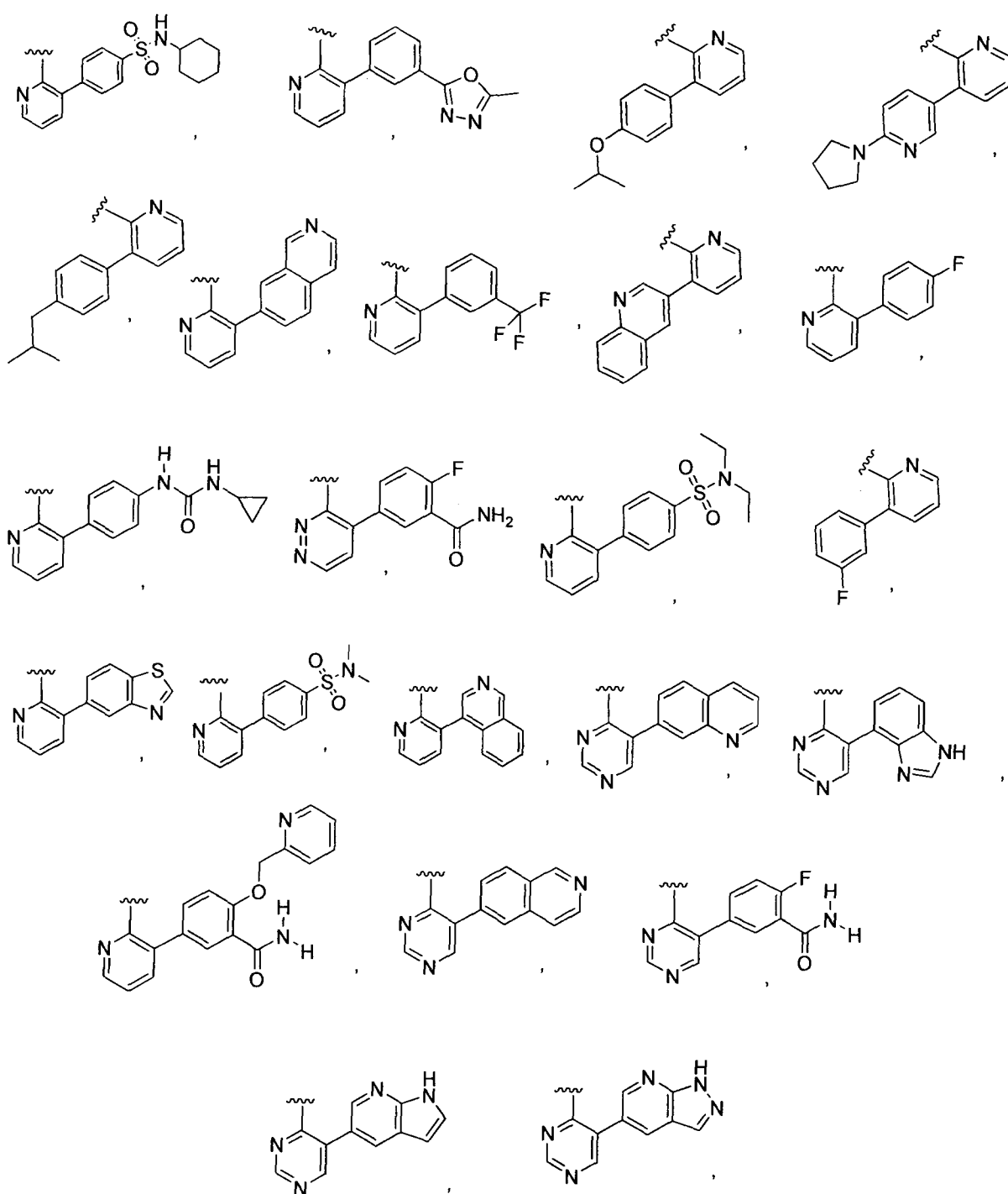
A specific value for A is:

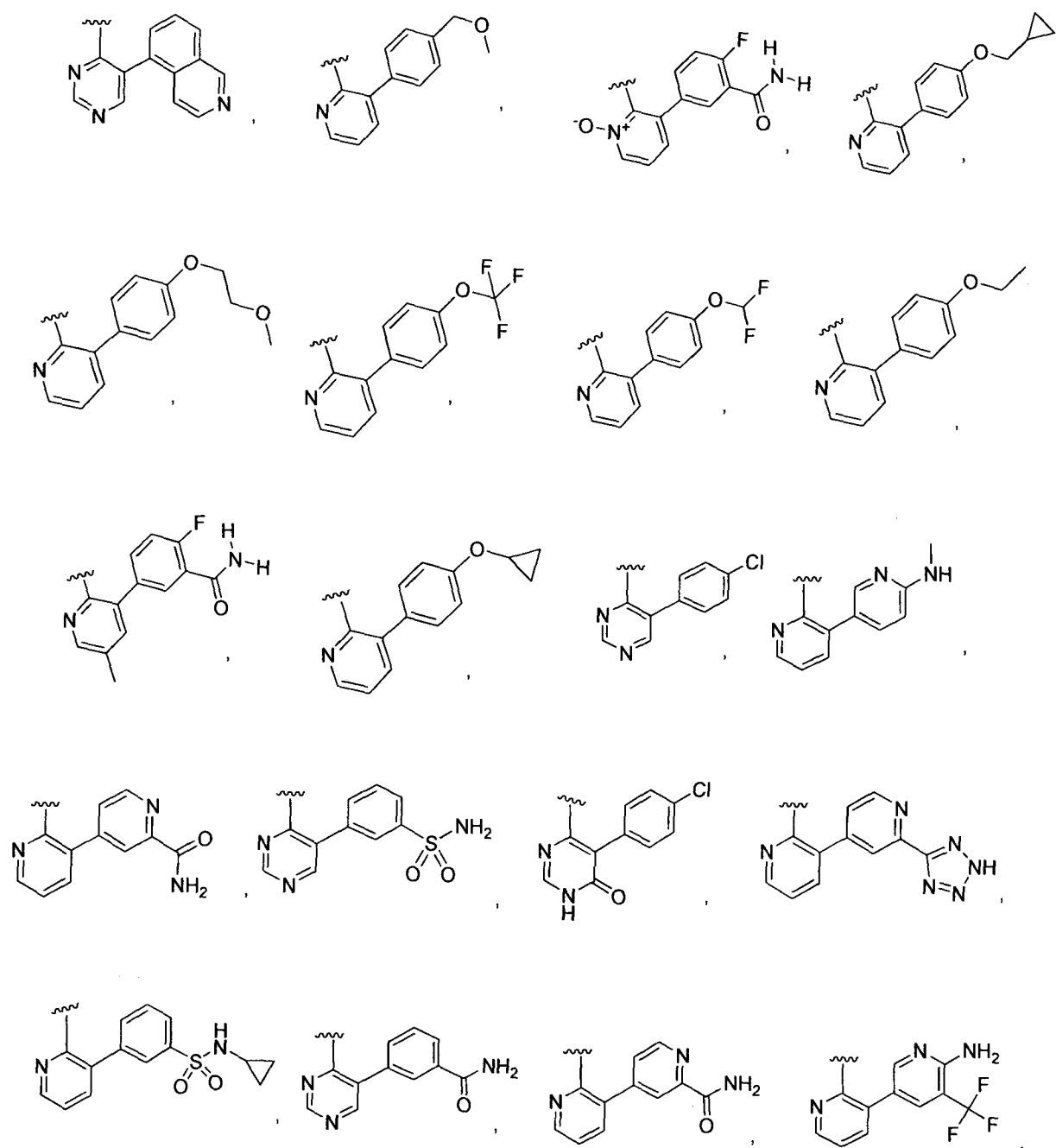


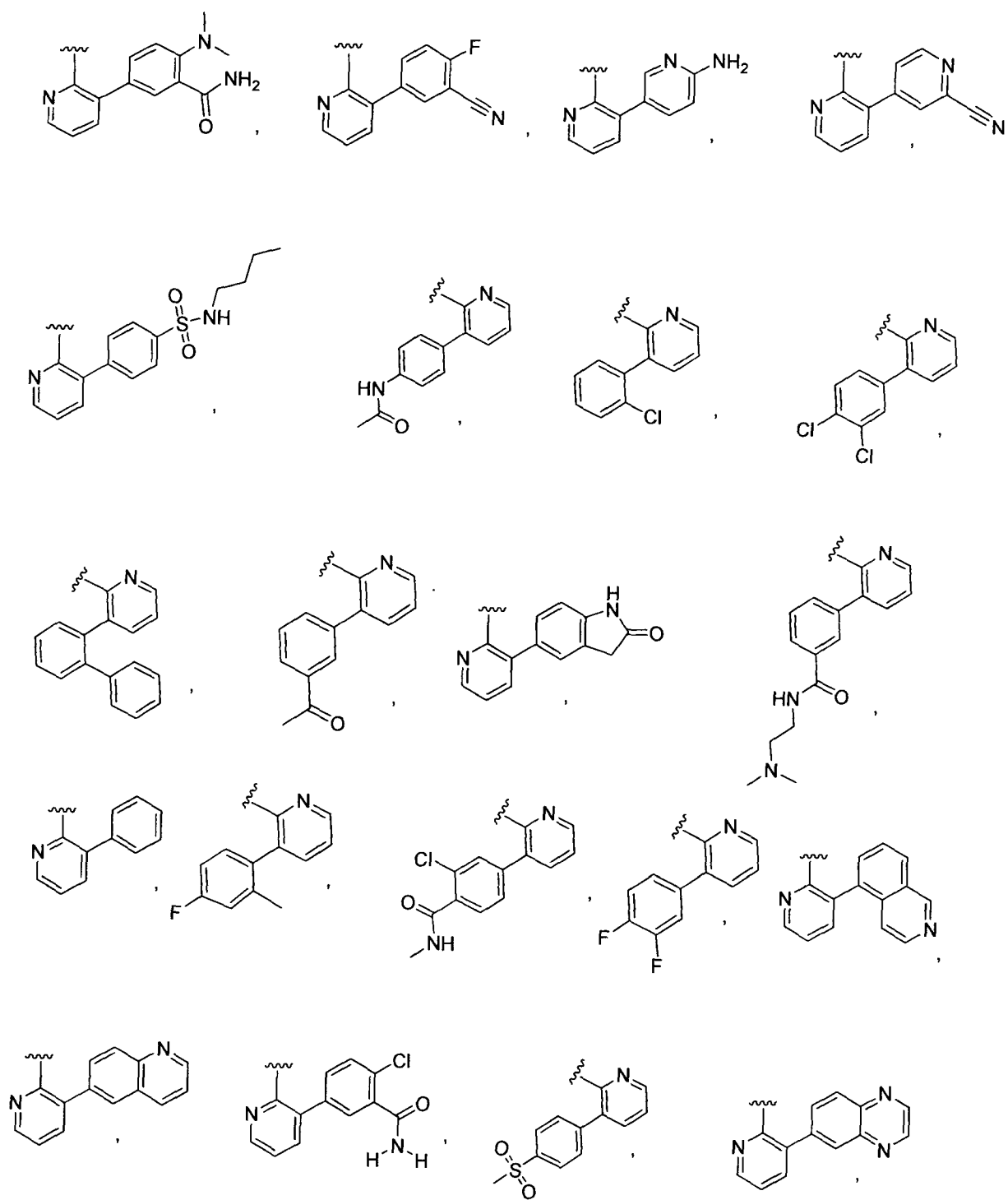
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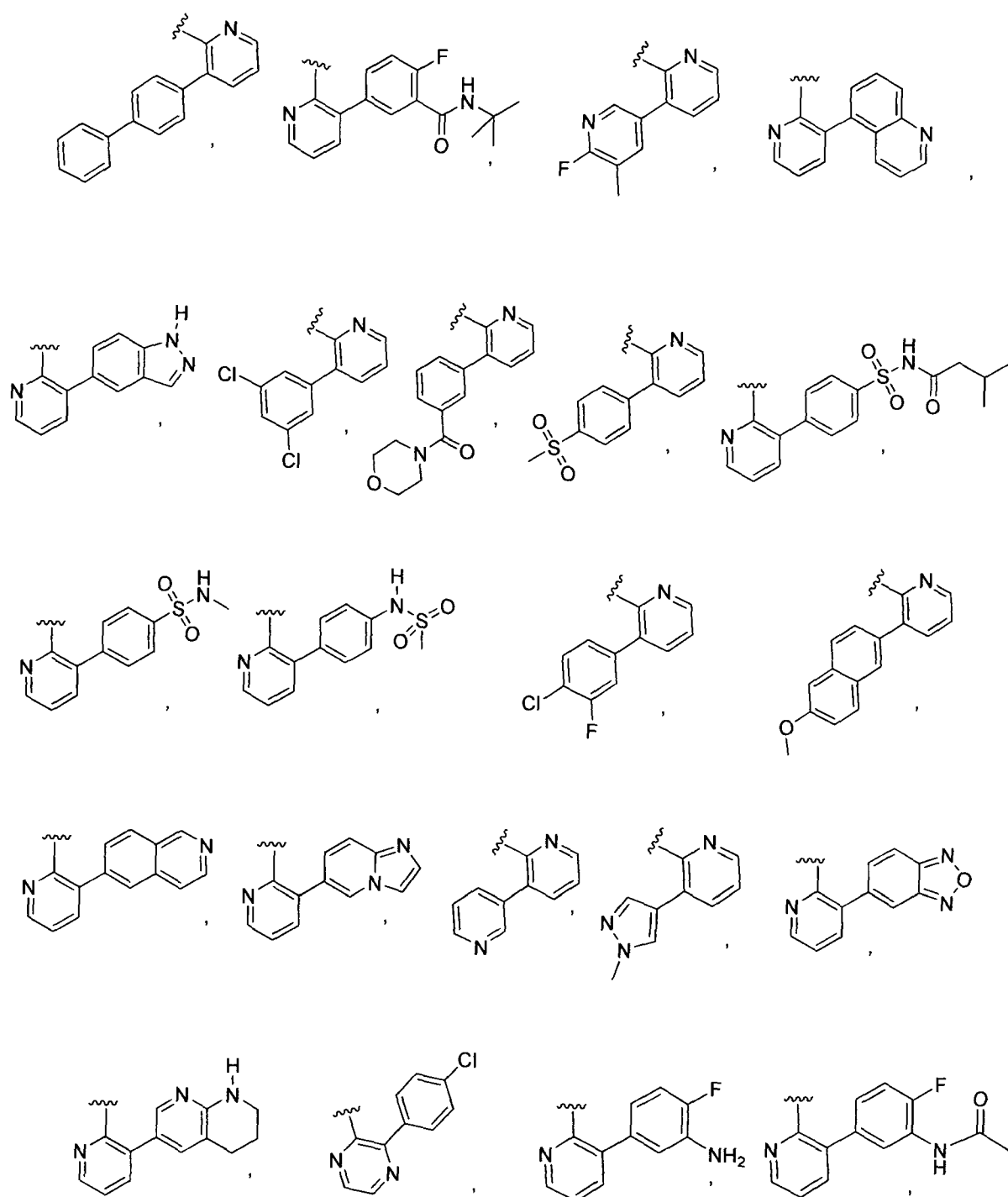


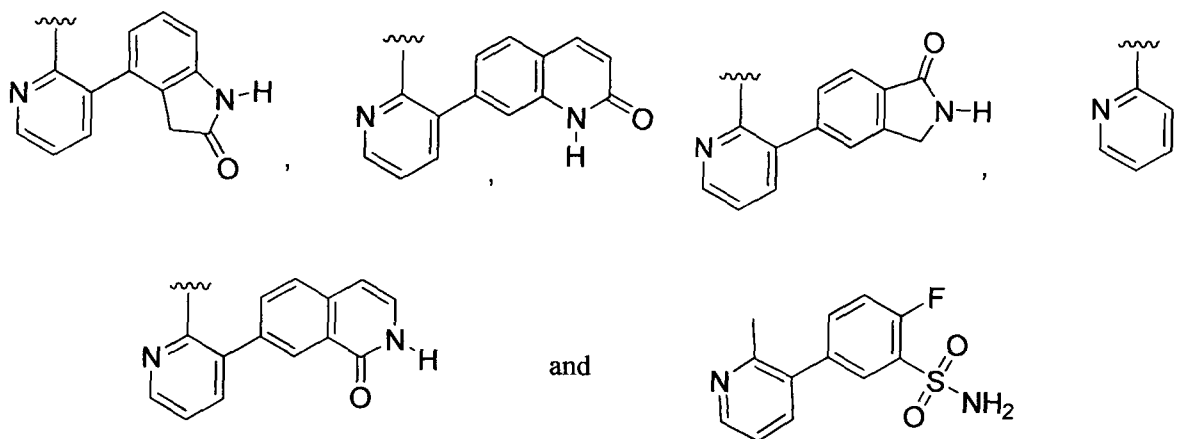












A specific value for R^1 is a value for R^1 as depicted in any or all of the examples as described herein below.

5 A specific value for R^2 is a value for R^2 as depicted in any or all of the examples as described herein below.

A specific value for W is a value for W as depicted in any or all of the examples as described herein below.

A specific value for A is a value for A as depicted in any or all of the examples as
10 described herein below.

In one embodiment a compound of the invention is a compound of formula I as described in any or all of the examples as described herein below.

In one embodiment a compound of the invention is an isomer (e.g. stereoisomer such as an enantiomer or diastereomer) of a compound of formula I as described in any or all of the examples as described herein below.

In one embodiment a compound of the invention is a racemic mixture of a compound of formula I as described in any or all of the examples as described herein below.

In one embodiment a heteroaryl (multiple condensed ring system) is a ring system comprising 2, 3 or 4 rings.

20 In one embodiment a heteroaryl (multiple condensed ring system) is a ring system comprising 3 or 4 rings.

In one embodiment a heteroaryl (multiple condensed ring system) is a ring system comprising 2 or 3 rings.

In one embodiment a heteroaryl (multiple condensed ring system) is a ring system
25 comprising 2 rings.

In one embodiment a heteroaryl (multiple condensed ring system) is a ring system

comprising 3 rings.

In one embodiment a heteroaryl (multiple condensed ring system) is a ring system comprising 4 rings.

In one embodiment a heterocycle (multiple condensed ring system) is a ring system
5 comprising 2, 3 or 4 rings.

In one embodiment a heterocycle (multiple condensed ring system) is a ring system comprising 3 or 4 rings.

In one embodiment a heterocycle (multiple condensed ring system) is a ring system comprising 2 or 3 rings.

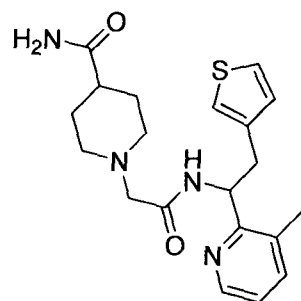
10 In one embodiment a heterocycle (multiple condensed ring system) is a ring system comprising 2 rings.

In one embodiment a heterocycle (multiple condensed ring system) is a ring system comprising 3 rings.

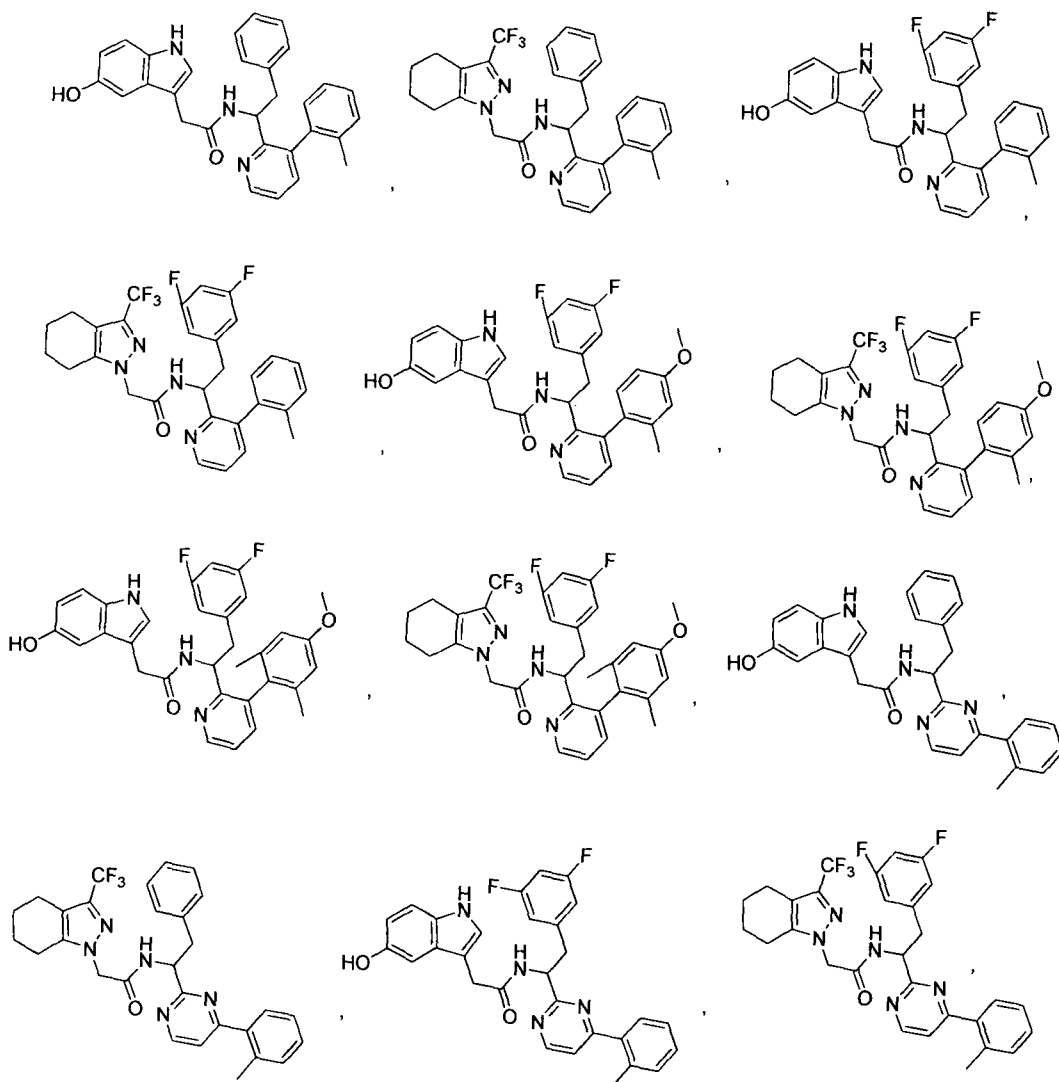
15 In one embodiment a heterocycle (multiple condensed ring system) is a ring system comprising 4 rings.

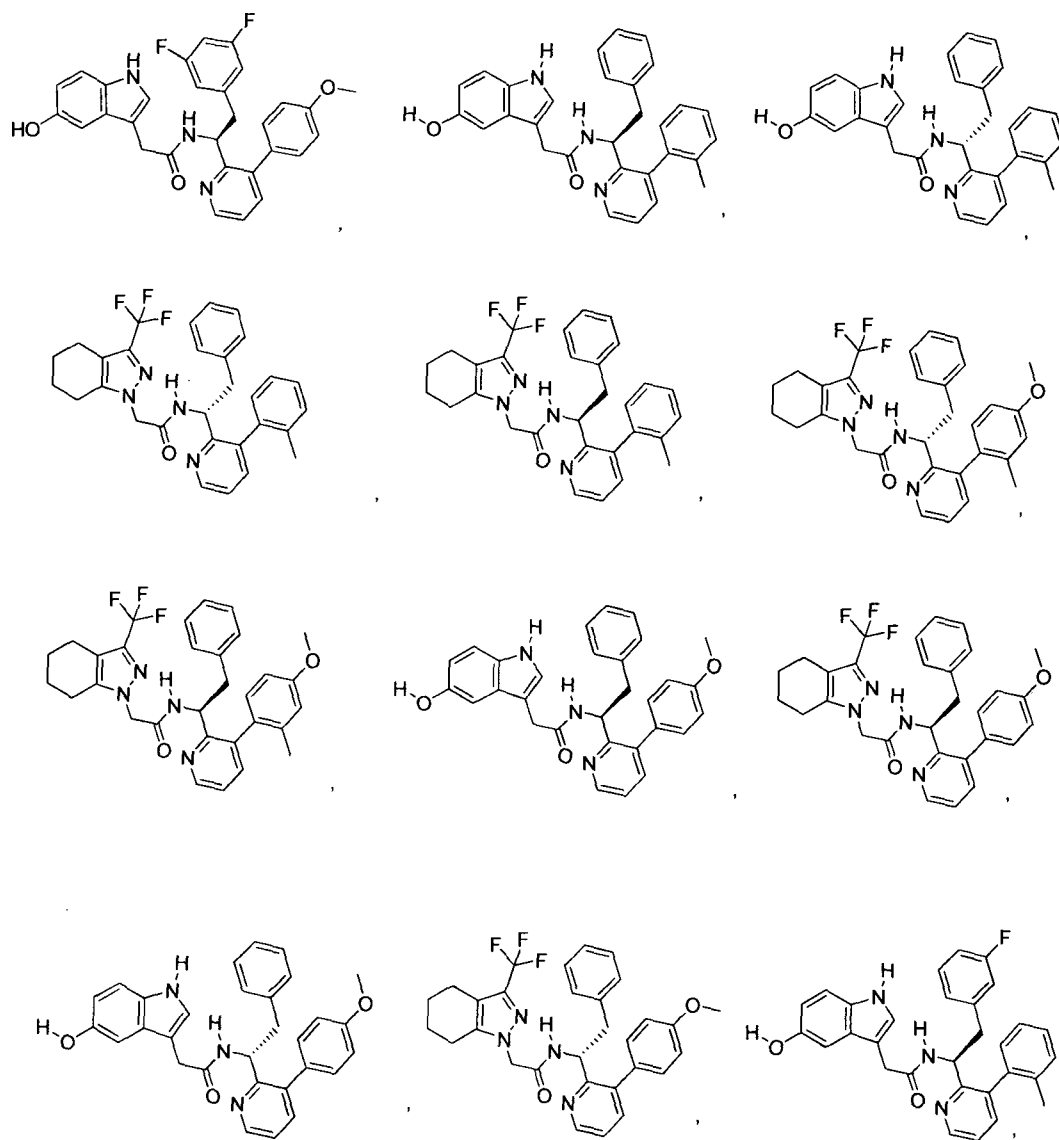
In one embodiment the term “carbocycle” or “carbocyclyl” refers to a single saturated (i.e., cycloalkyl) or a single partially unsaturated (e.g., cycloalkenyl, cycloalkadienyl, etc.) ring having 3 to 7 carbon atoms (i.e. (C₃-C₇)carbocycle). The term “carbocycle” or “carbocyclyl” also includes multiple condensed ring systems (e.g. ring systems comprising 2, 3 or 4
20 carbocyclic rings). Accordingly, carbocycle includes multicyclic carbocycles having 7 to 12 carbon atoms as a bicycle, and up to about 20 carbon atoms as a polycycle. Multicyclic carbocycles can be connected to each other via a single carbon atom to form a spiro connection (e.g. spiro[4,5]decane, spiro[4.5]decane, etc), via two adjacent carbon atoms to form a fused connection such as a bicyclo [4,5], [5,5], [5,6] or [6,6] system, or 9 or 10 ring
25 atoms arranged as a bicyclo [5,6] or [6,6] system (e.g. 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-
30 cyclopent-3-enyl, cyclohexyl, 1-cyclohex-1-enyl, 1-cyclohex-2-enyl and 1-cyclohex-3-enyl.

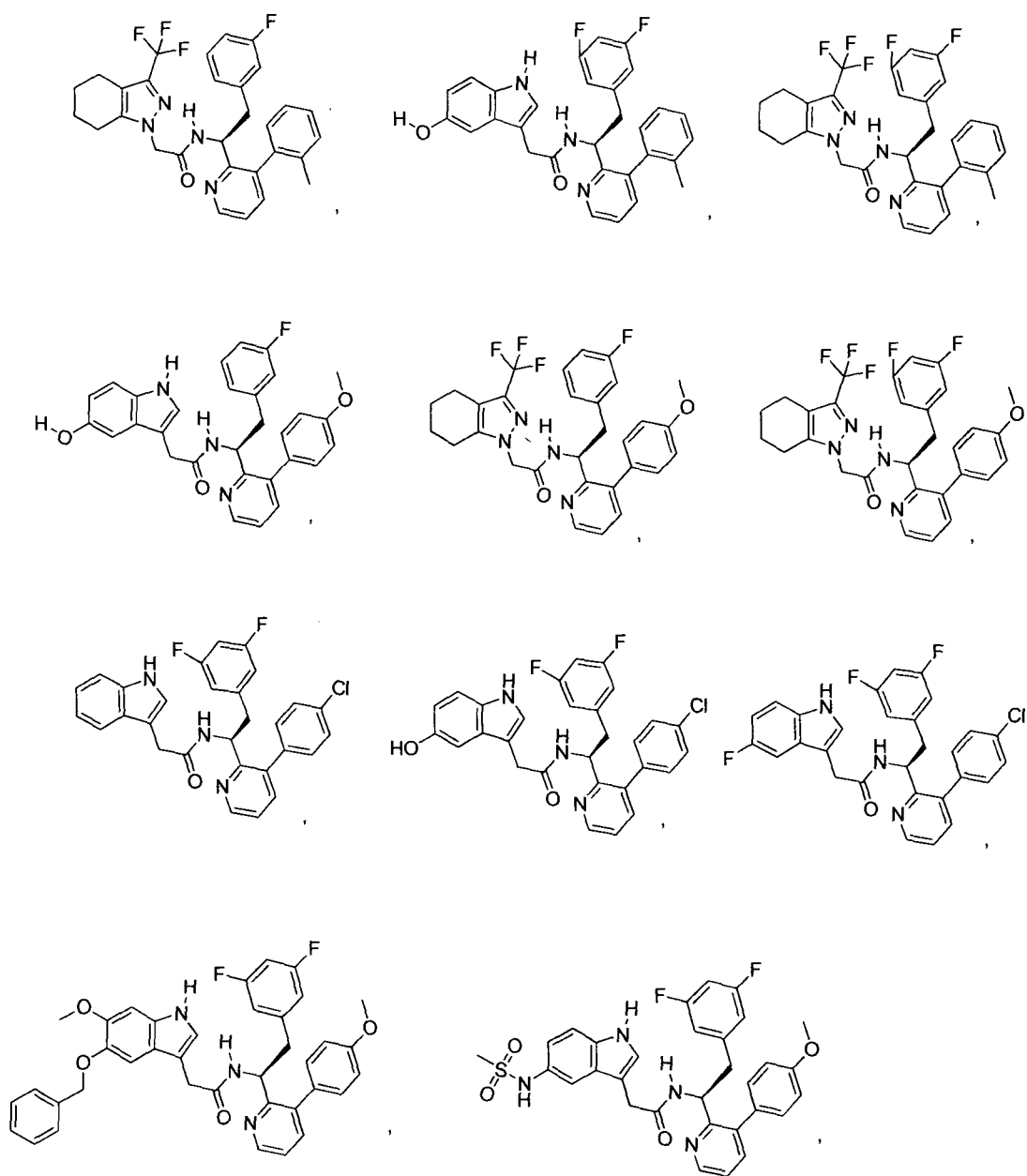
In one embodiment the compounds of formula I do not include the compound:

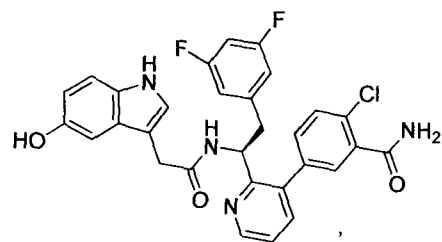
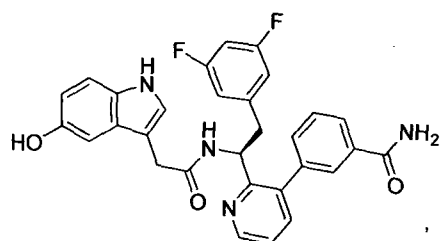
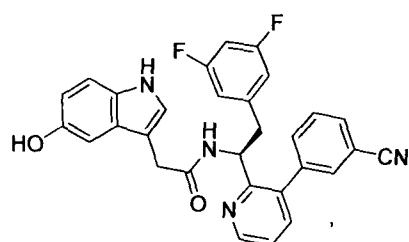
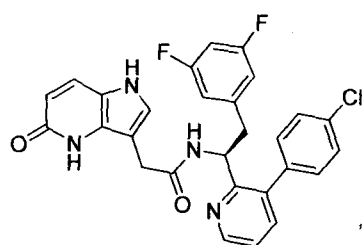
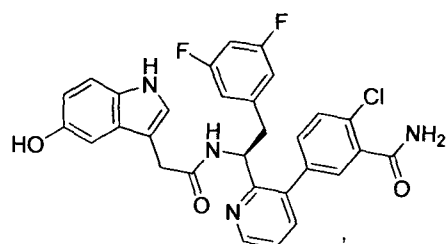
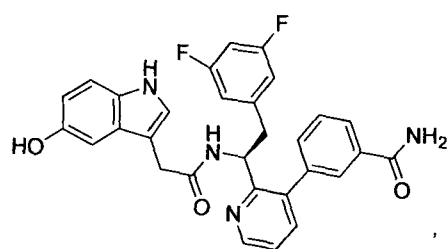
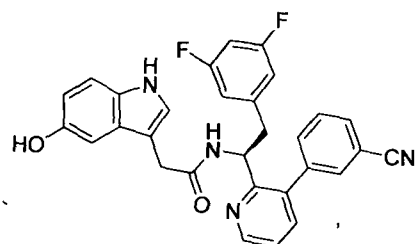
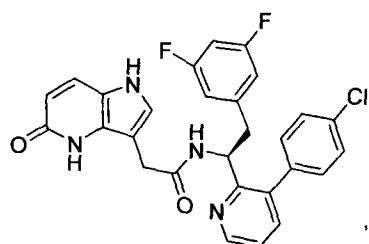
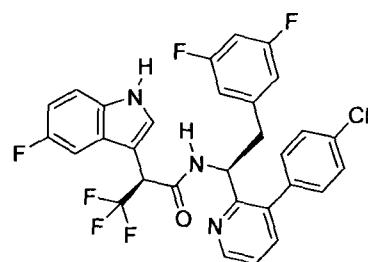
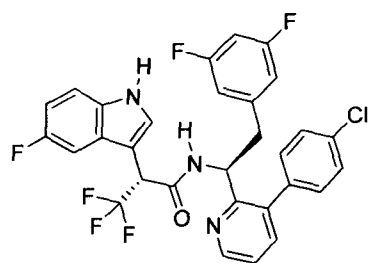


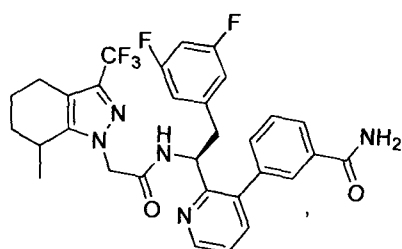
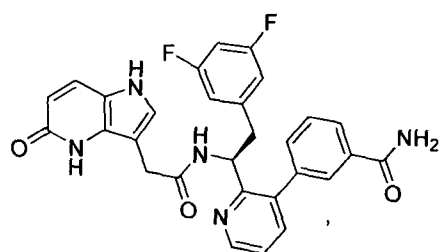
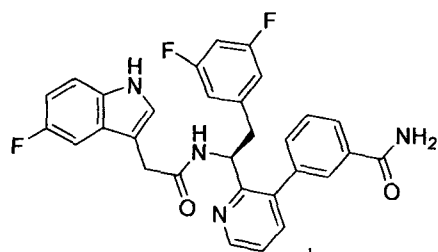
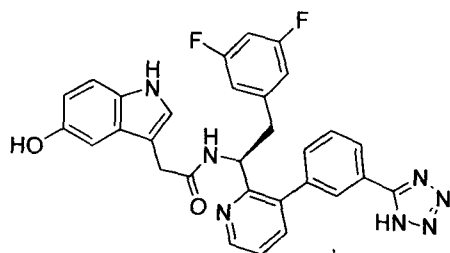
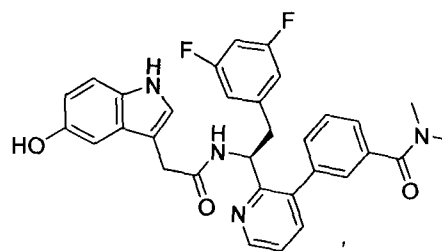
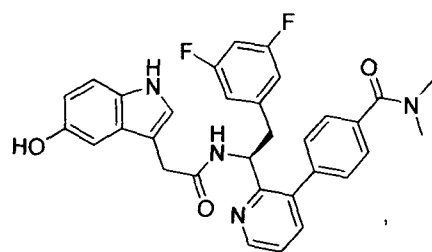
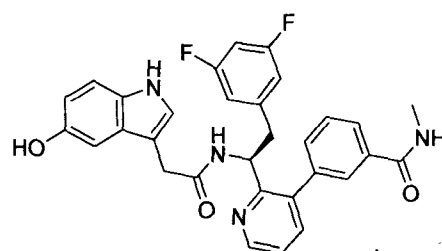
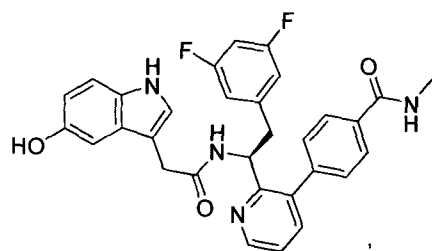
In one embodiment the compounds of formula I include:



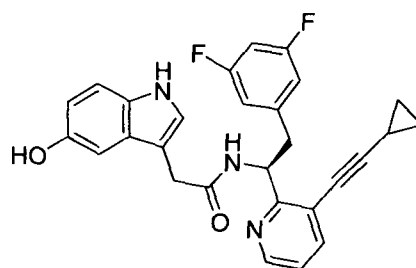






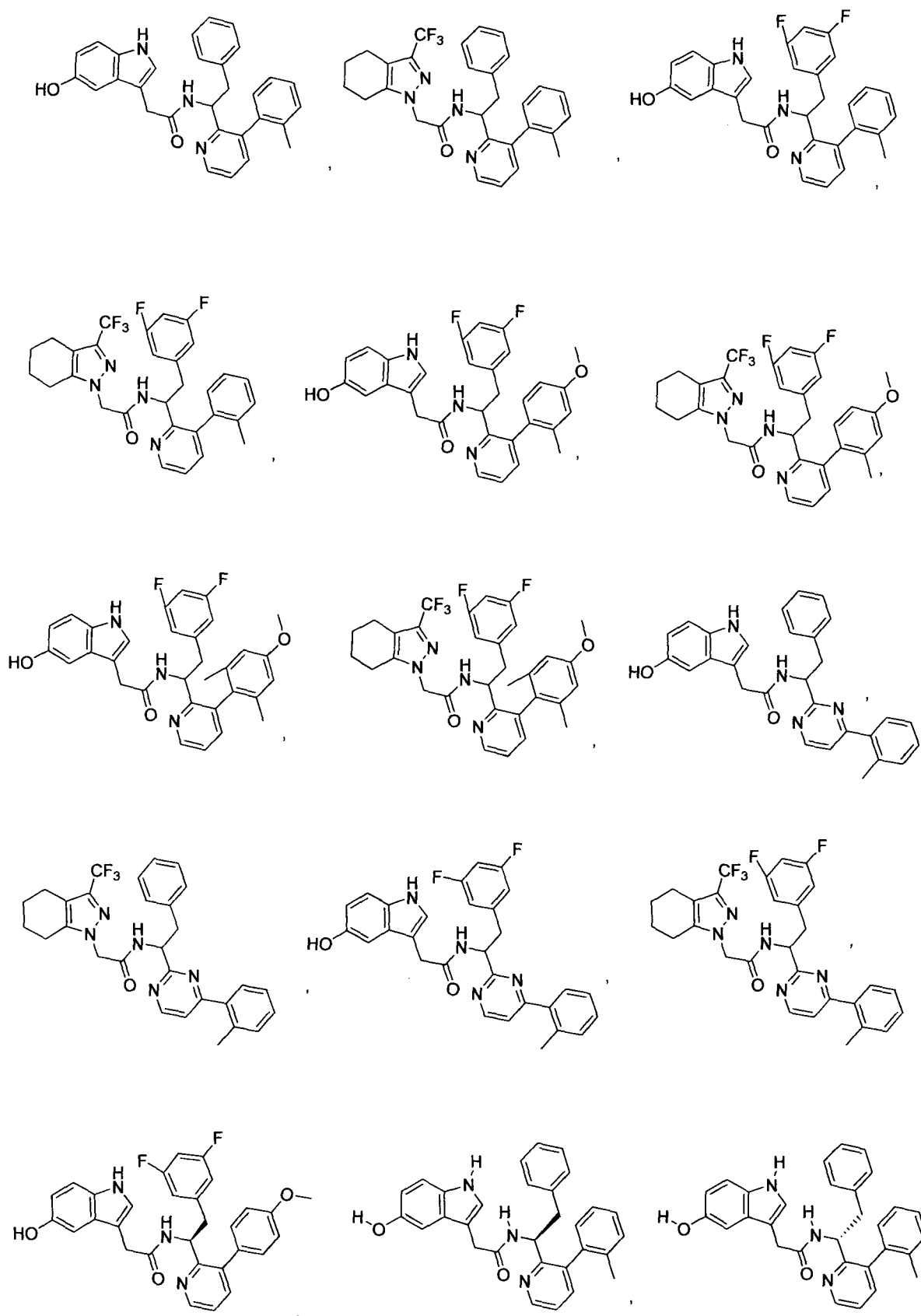


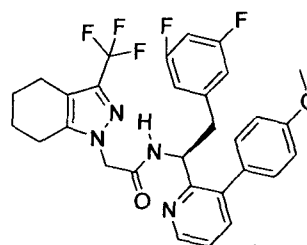
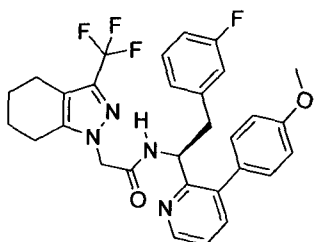
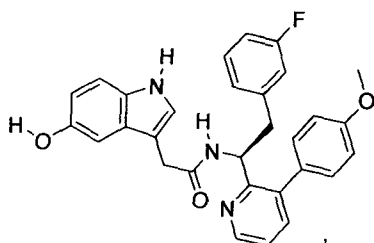
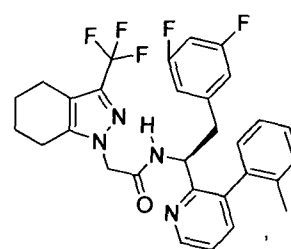
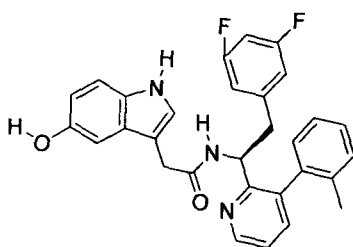
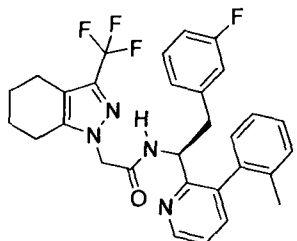
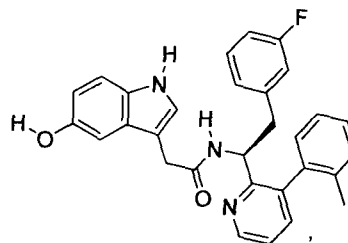
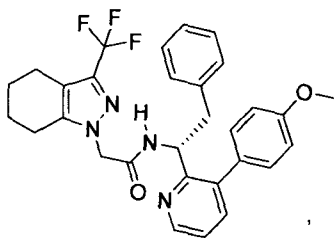
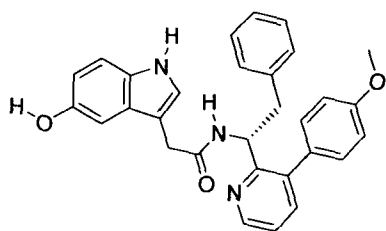
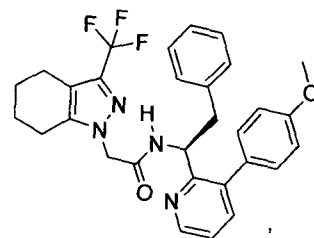
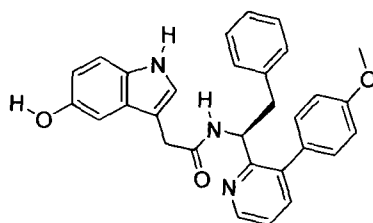
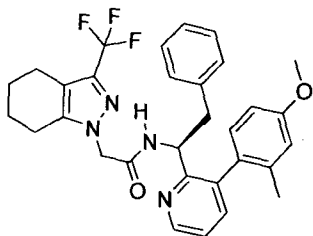
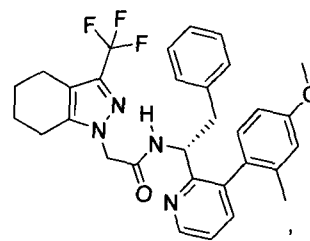
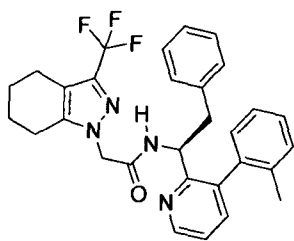
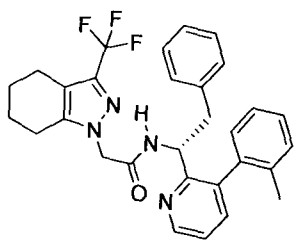
and

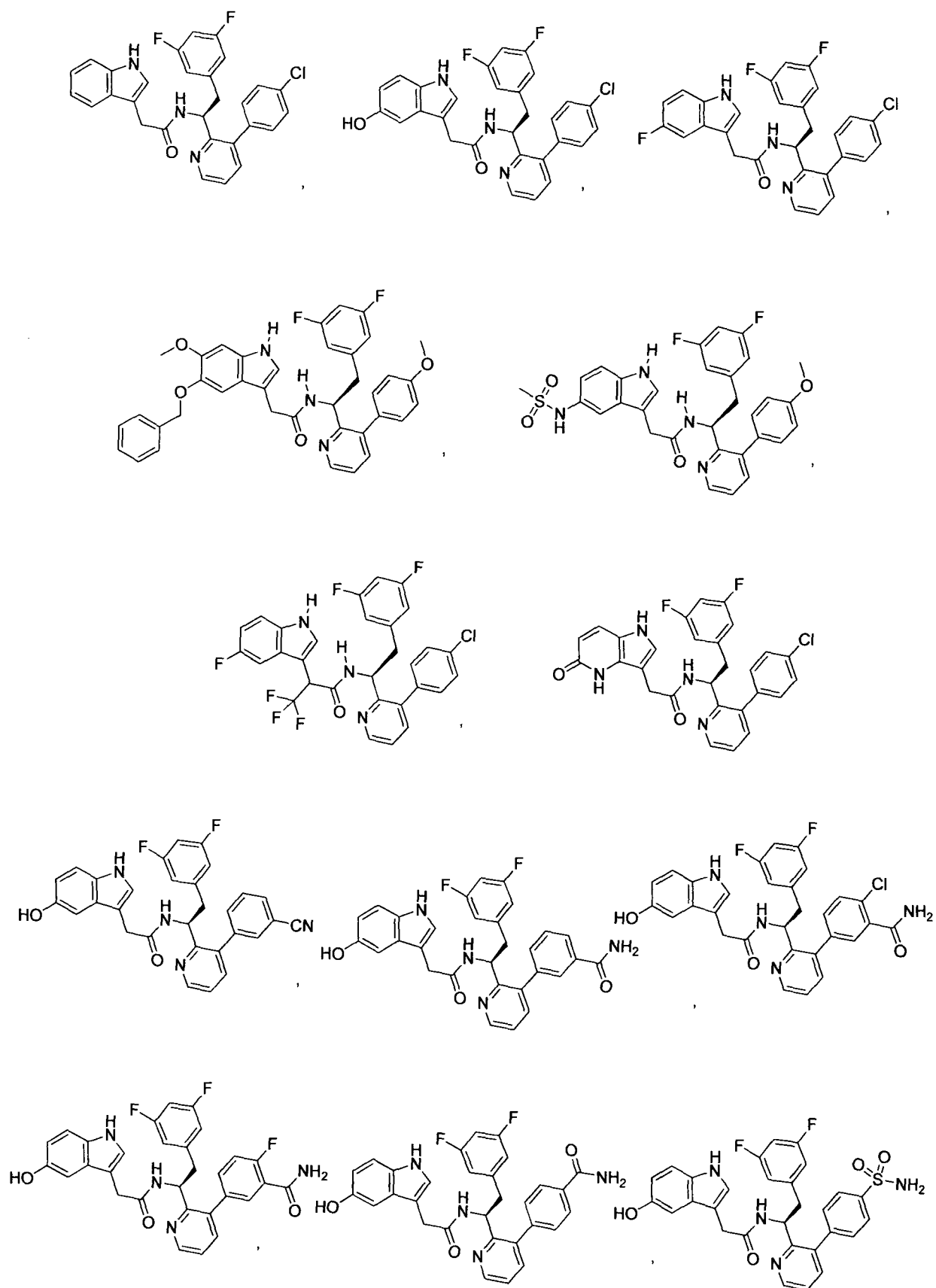


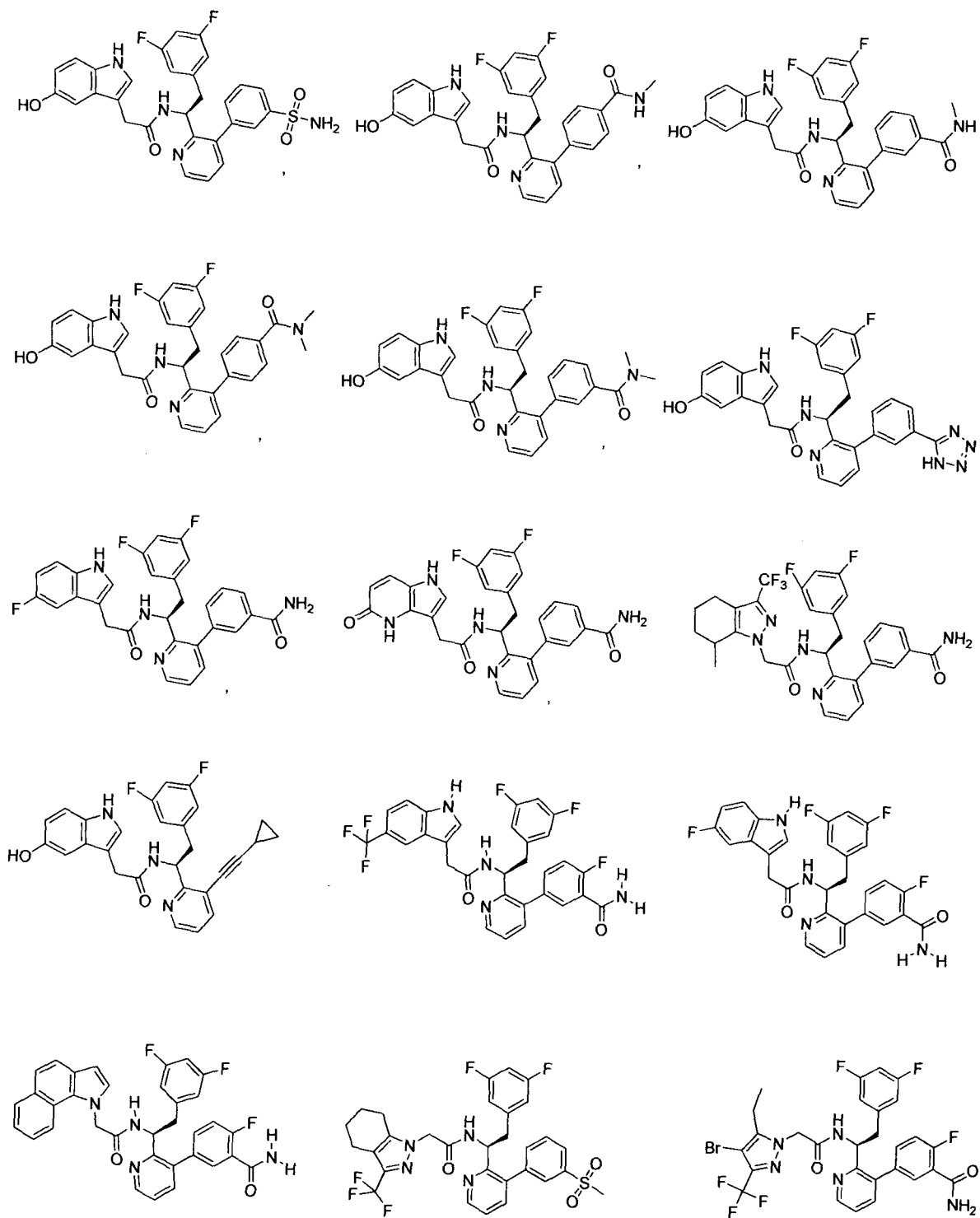
and salts thereof.

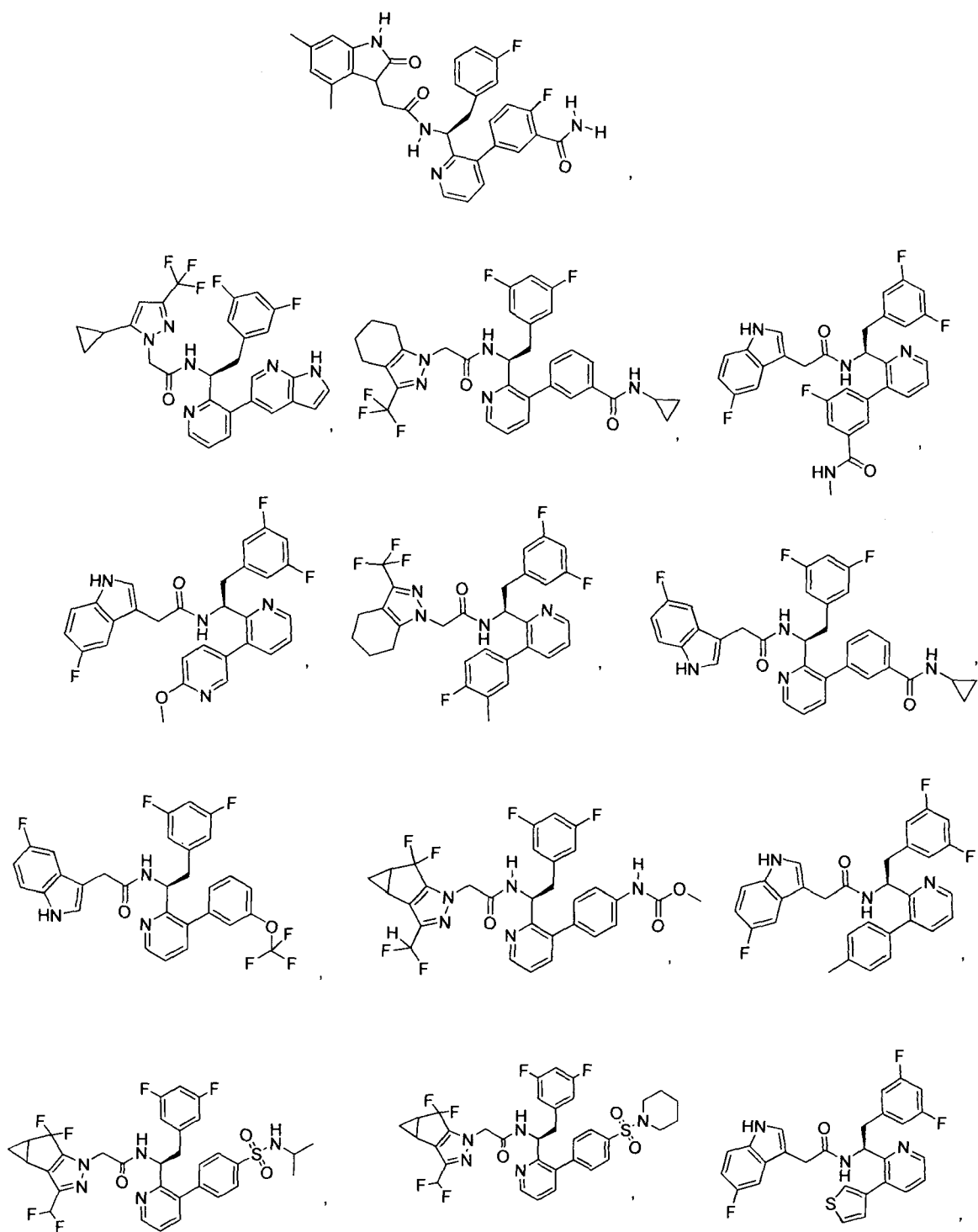
In one embodiment the compounds of formula I include:

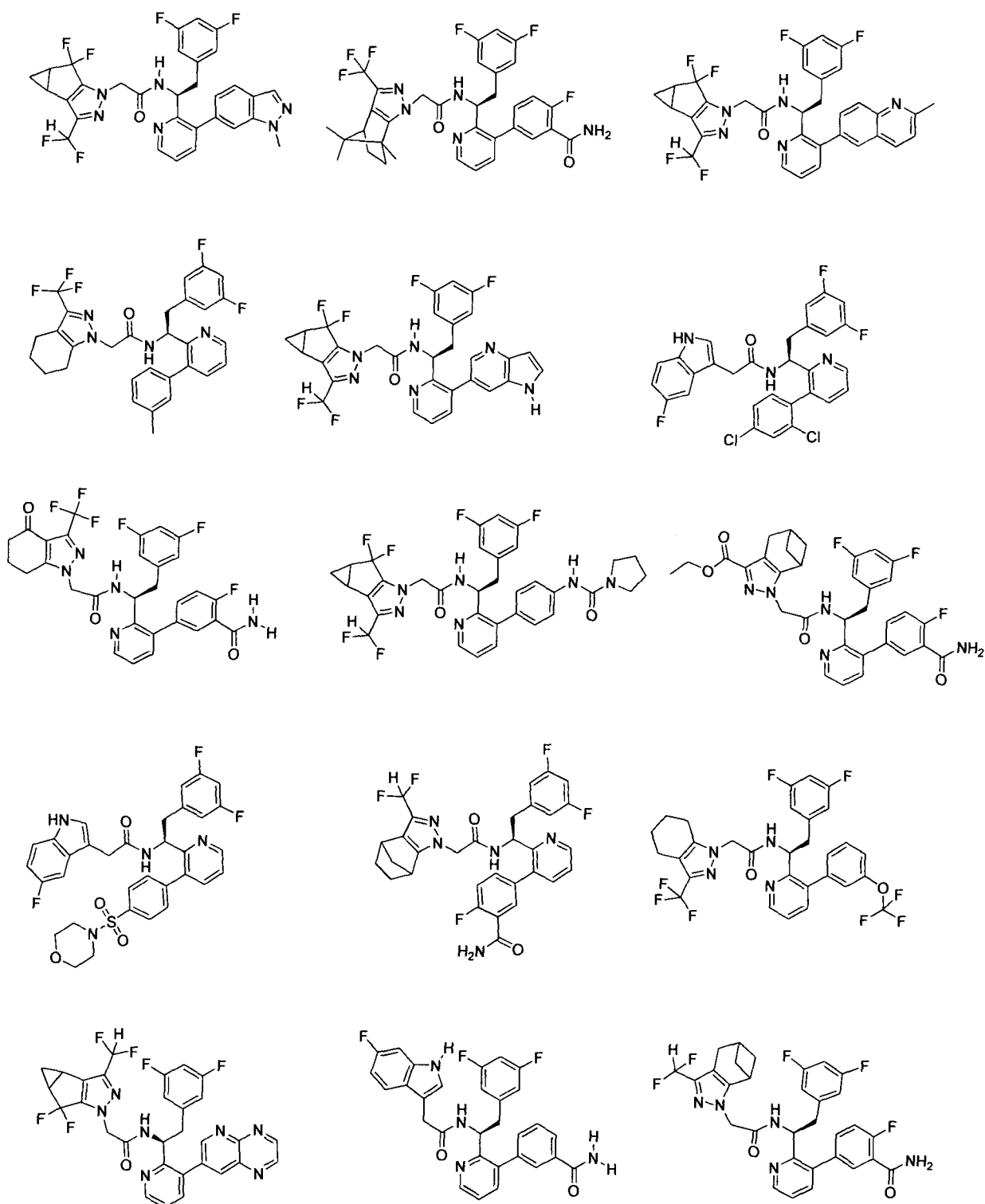


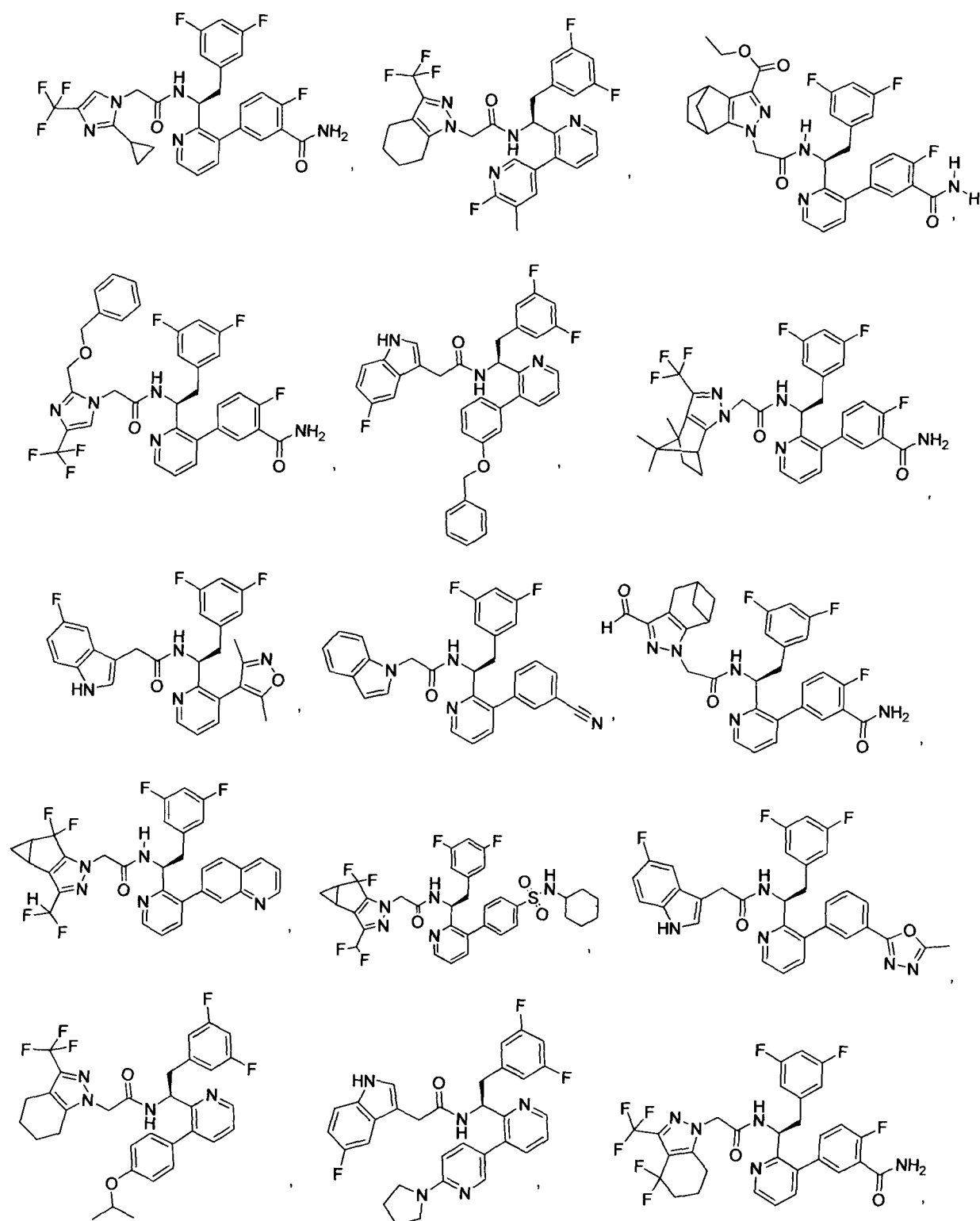


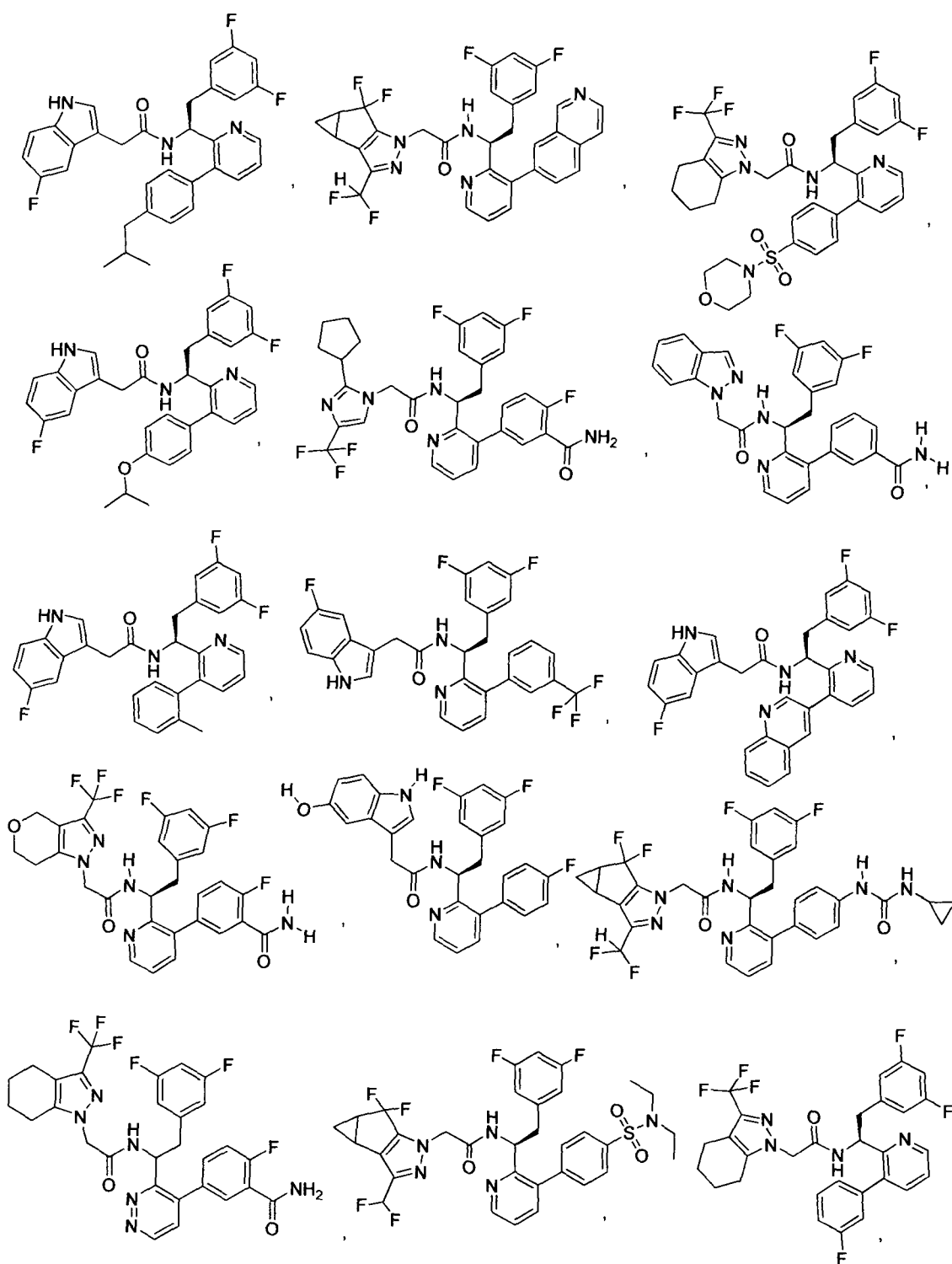


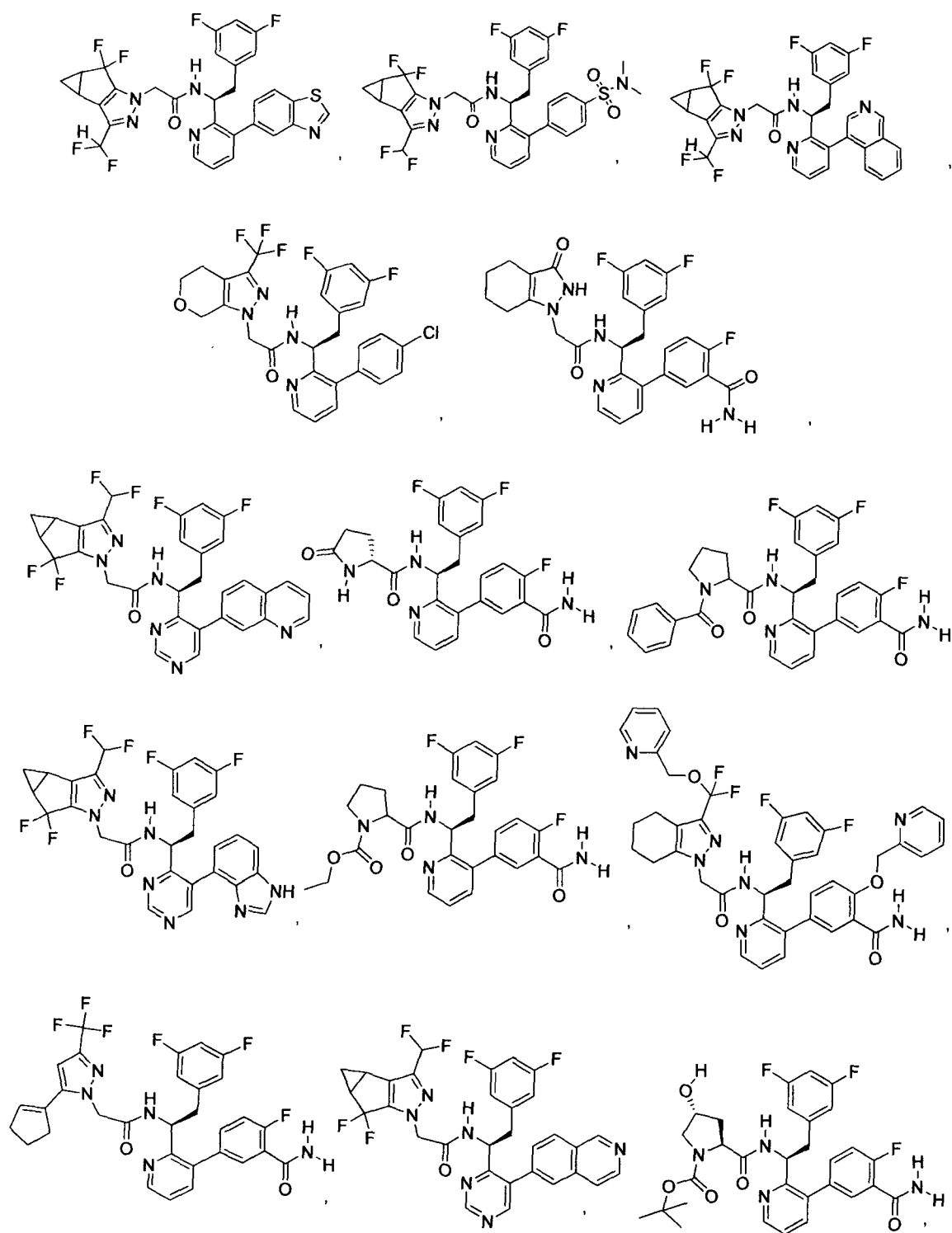


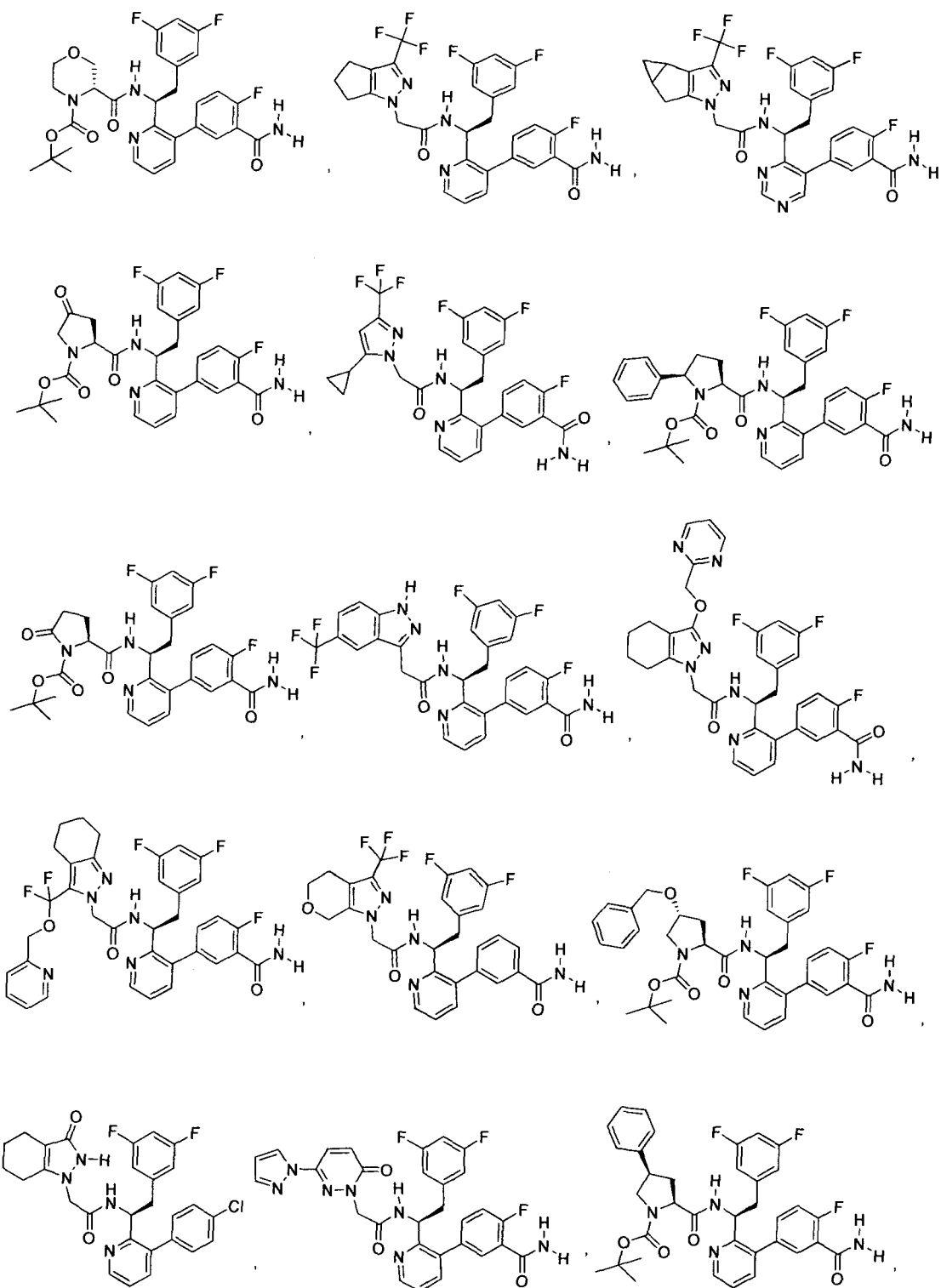


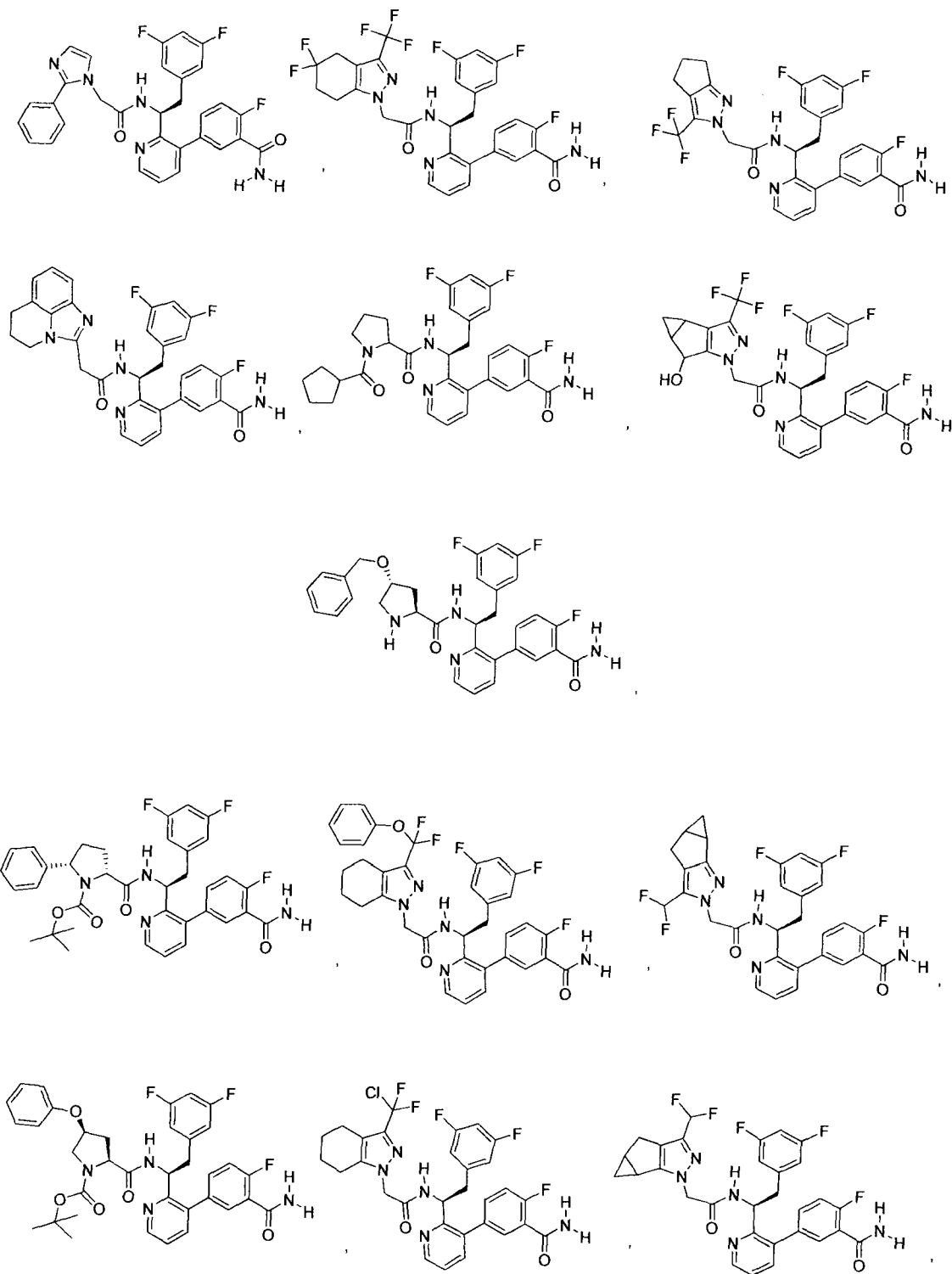


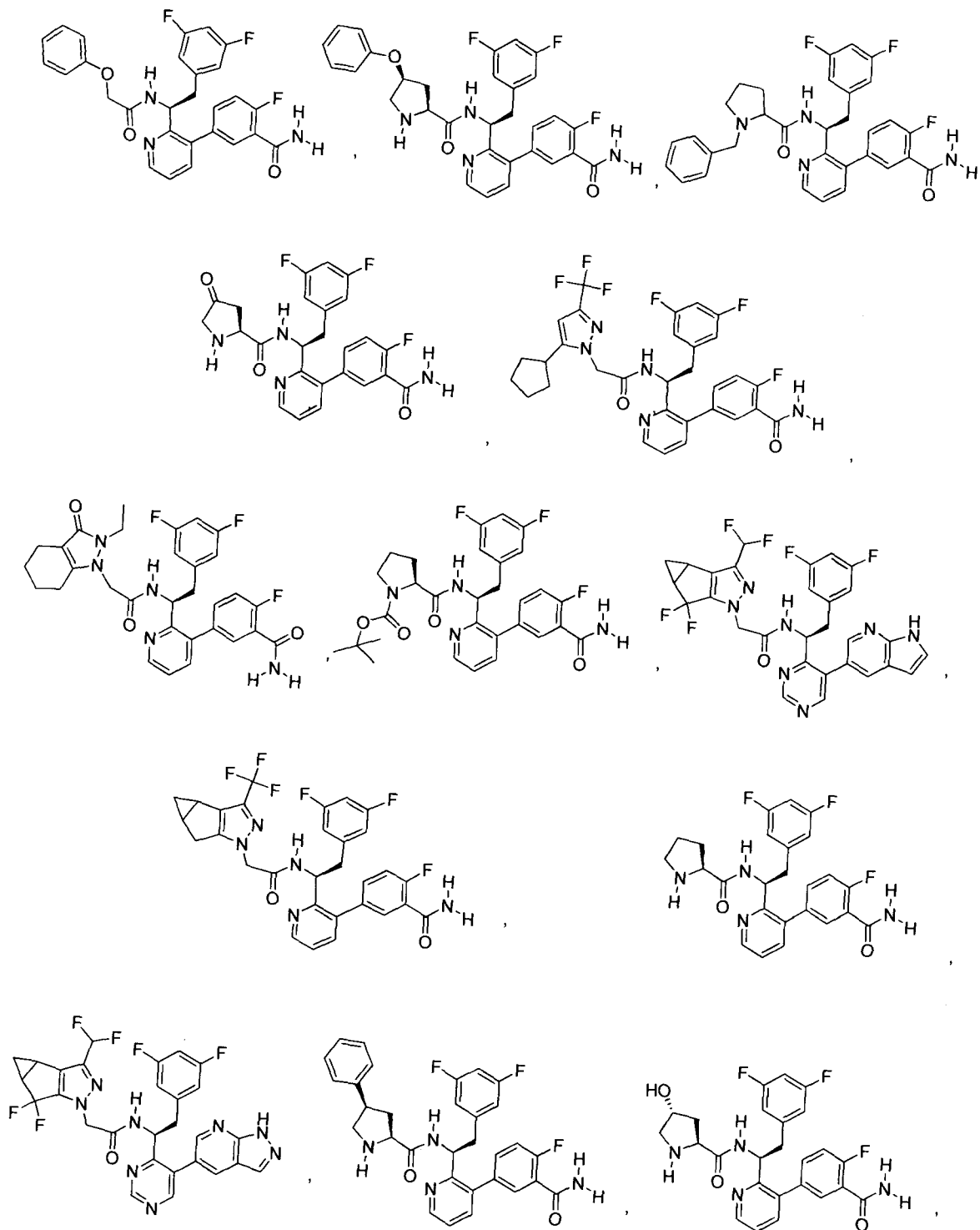


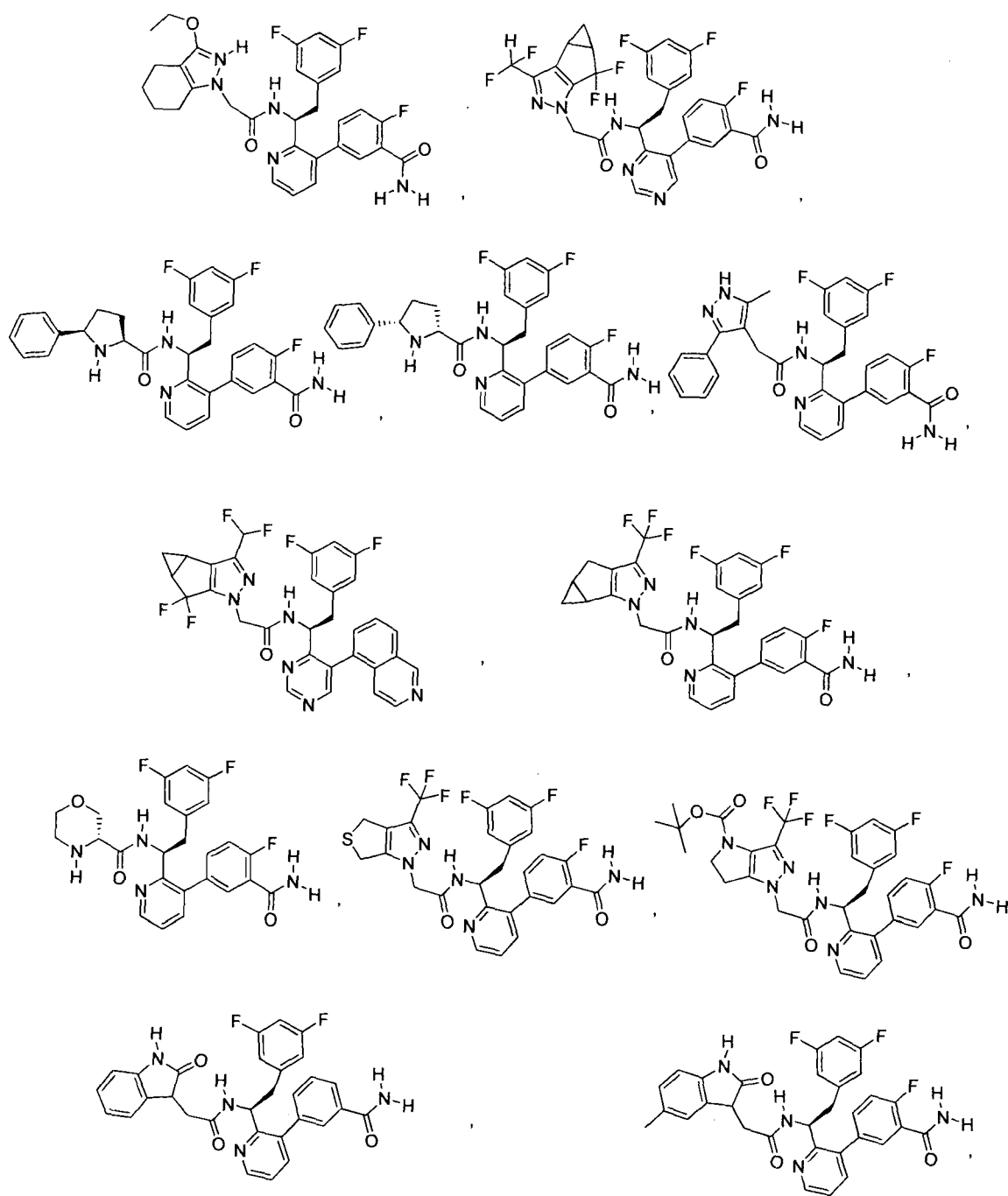


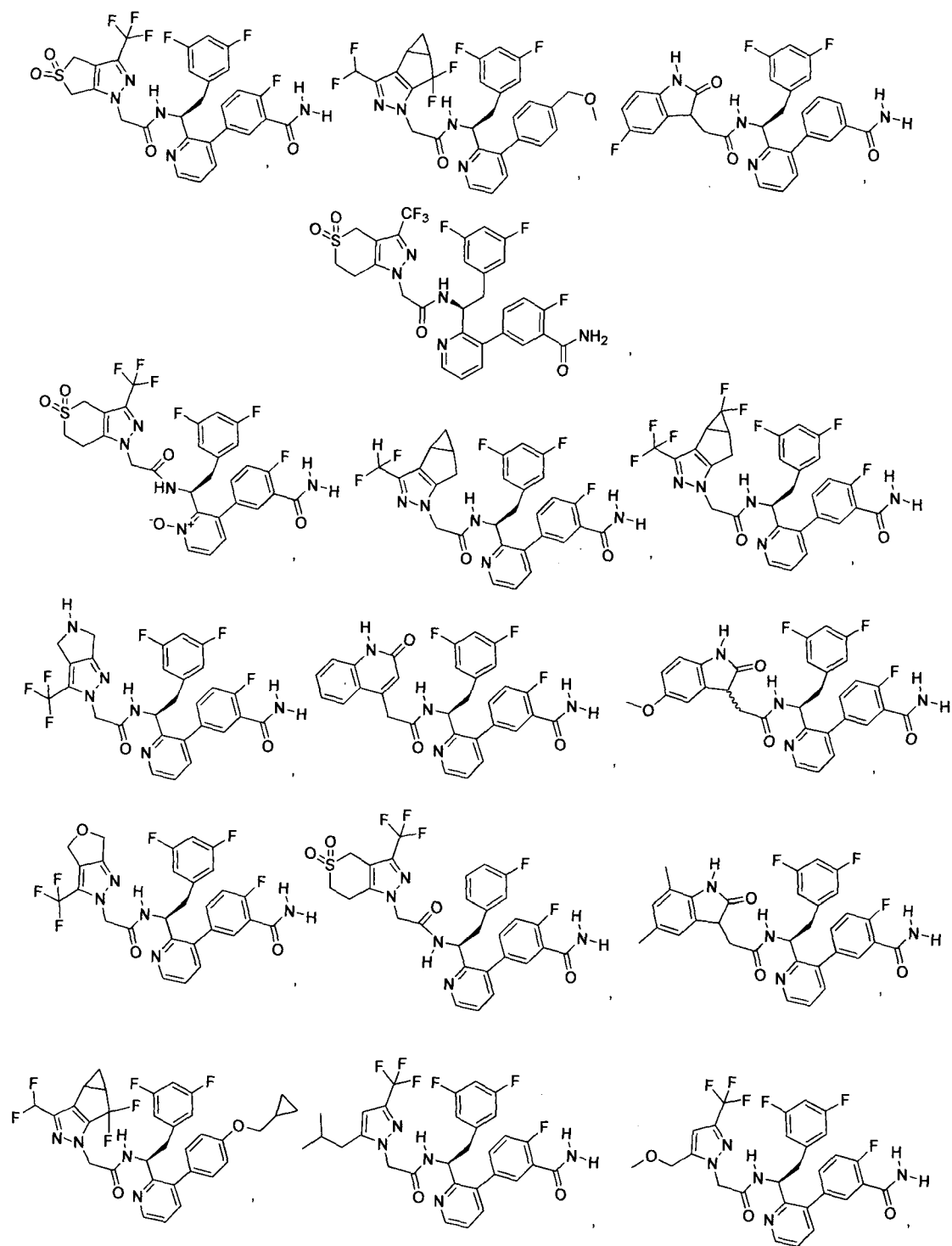


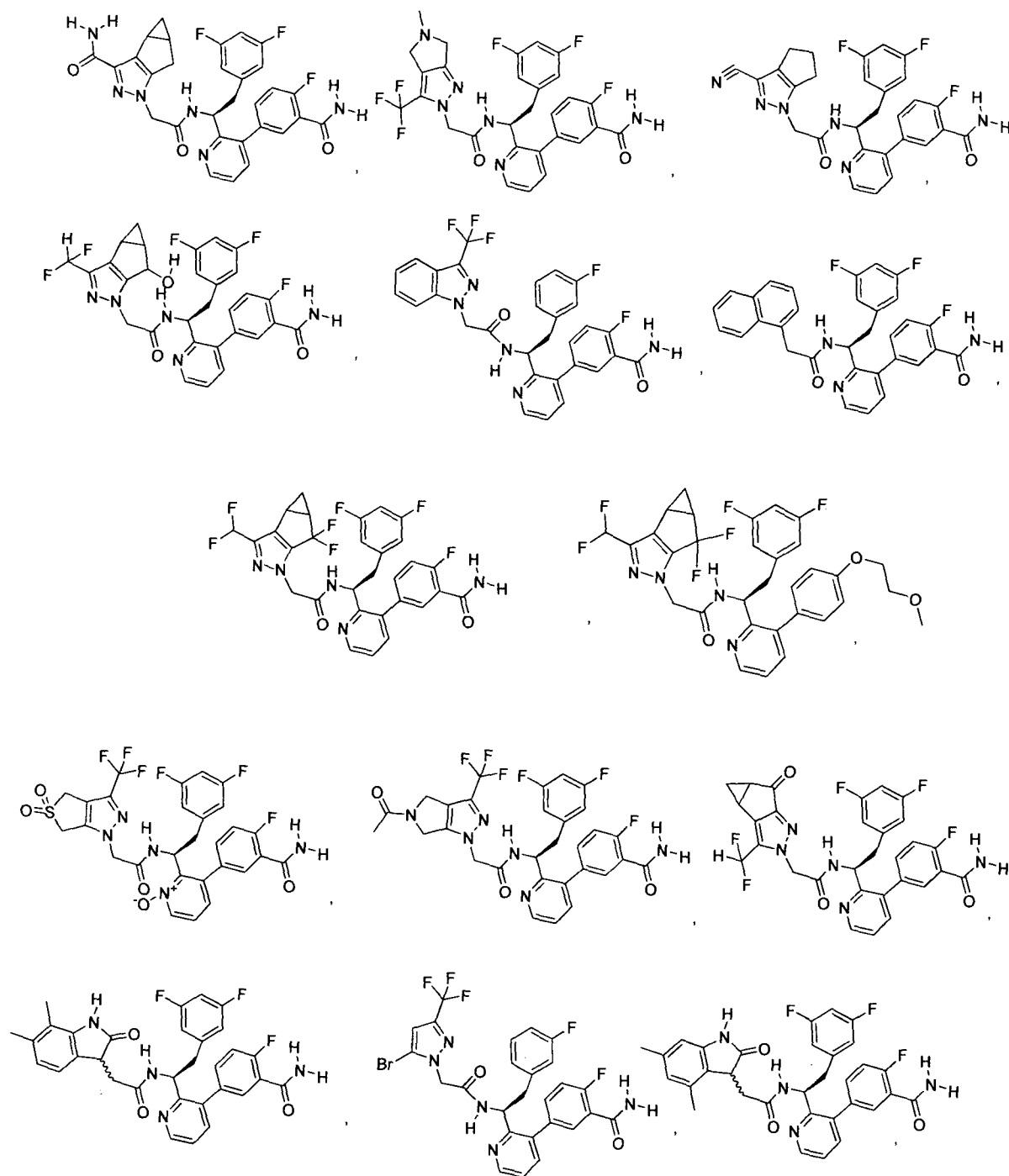


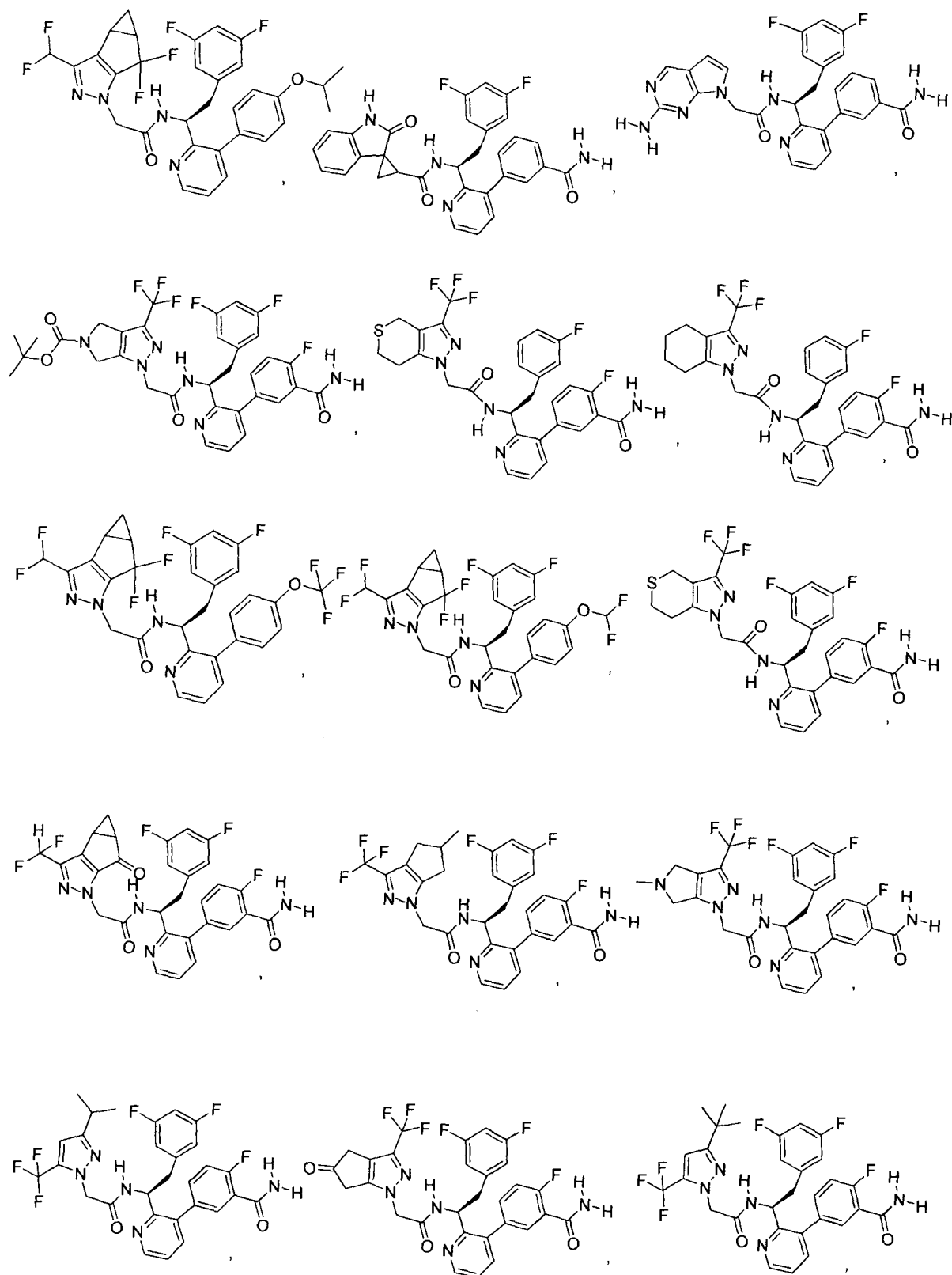


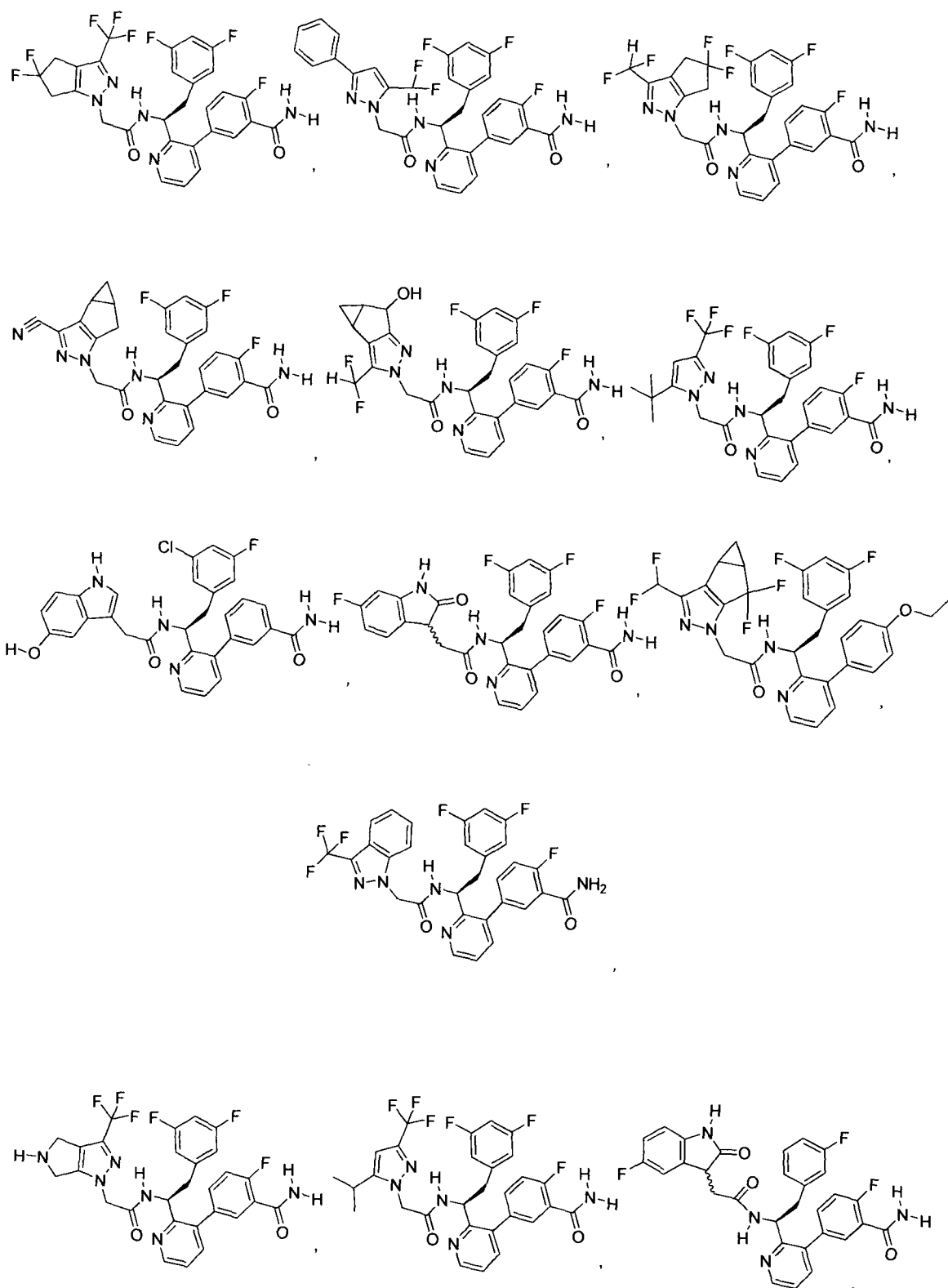


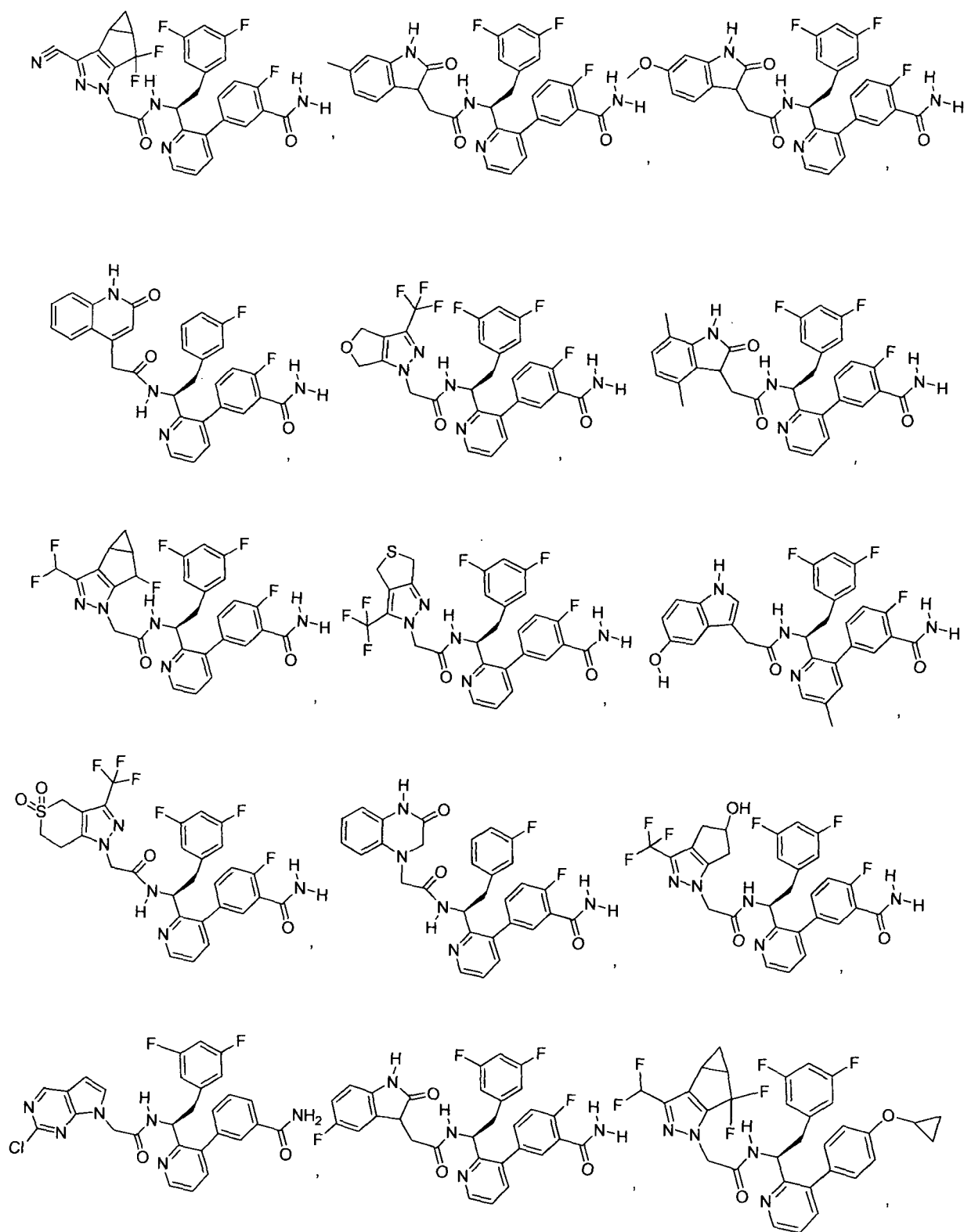


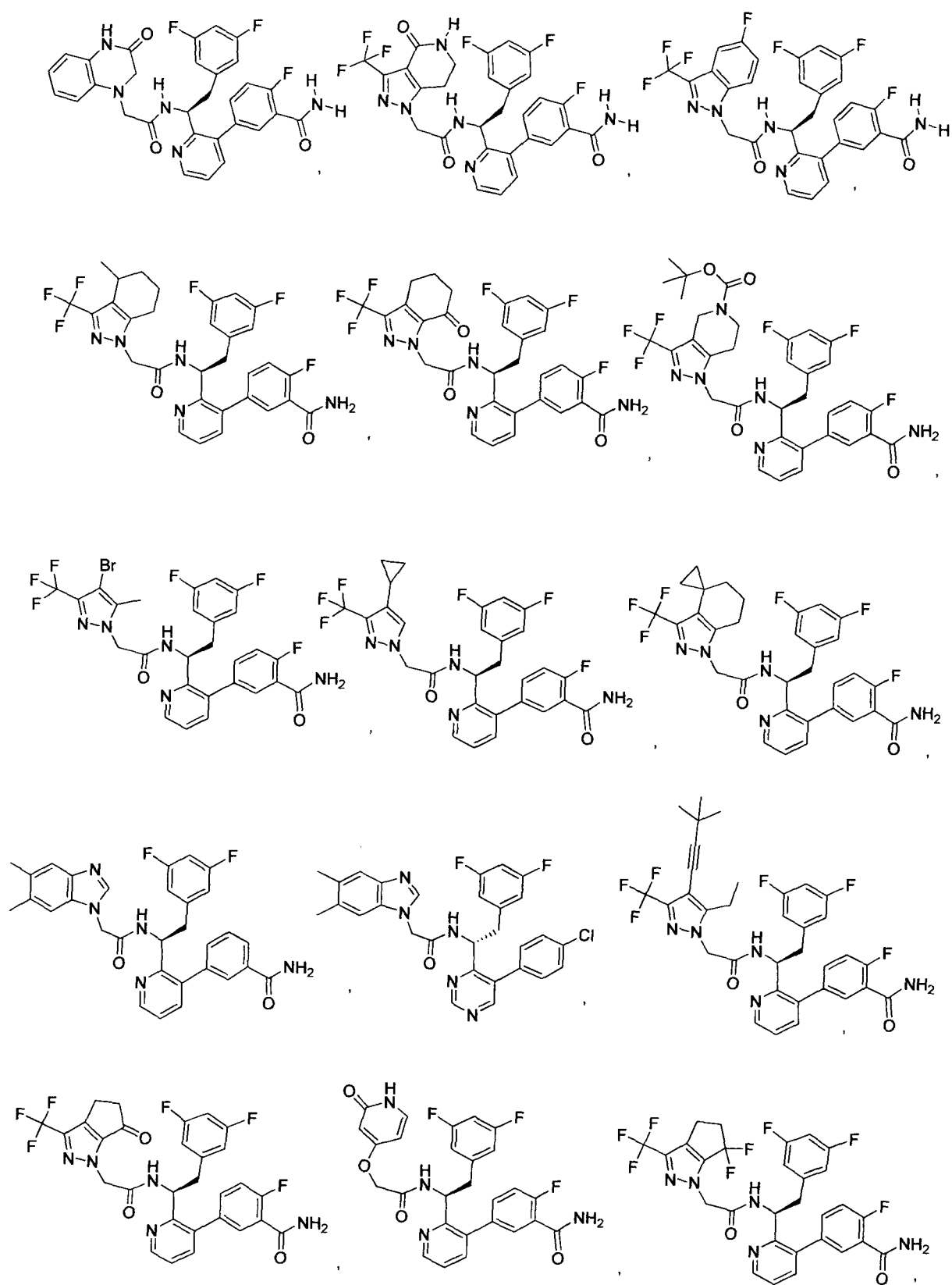


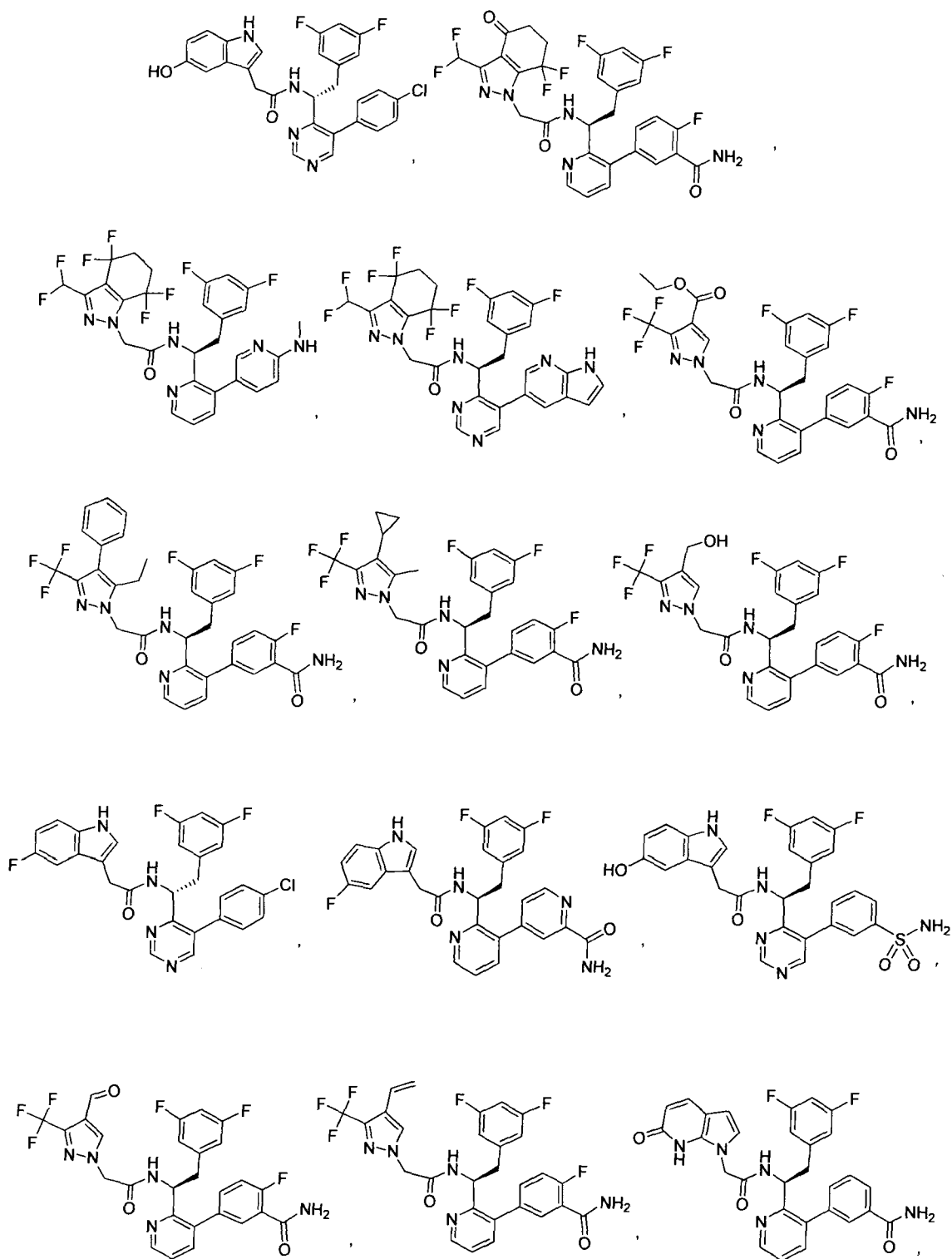


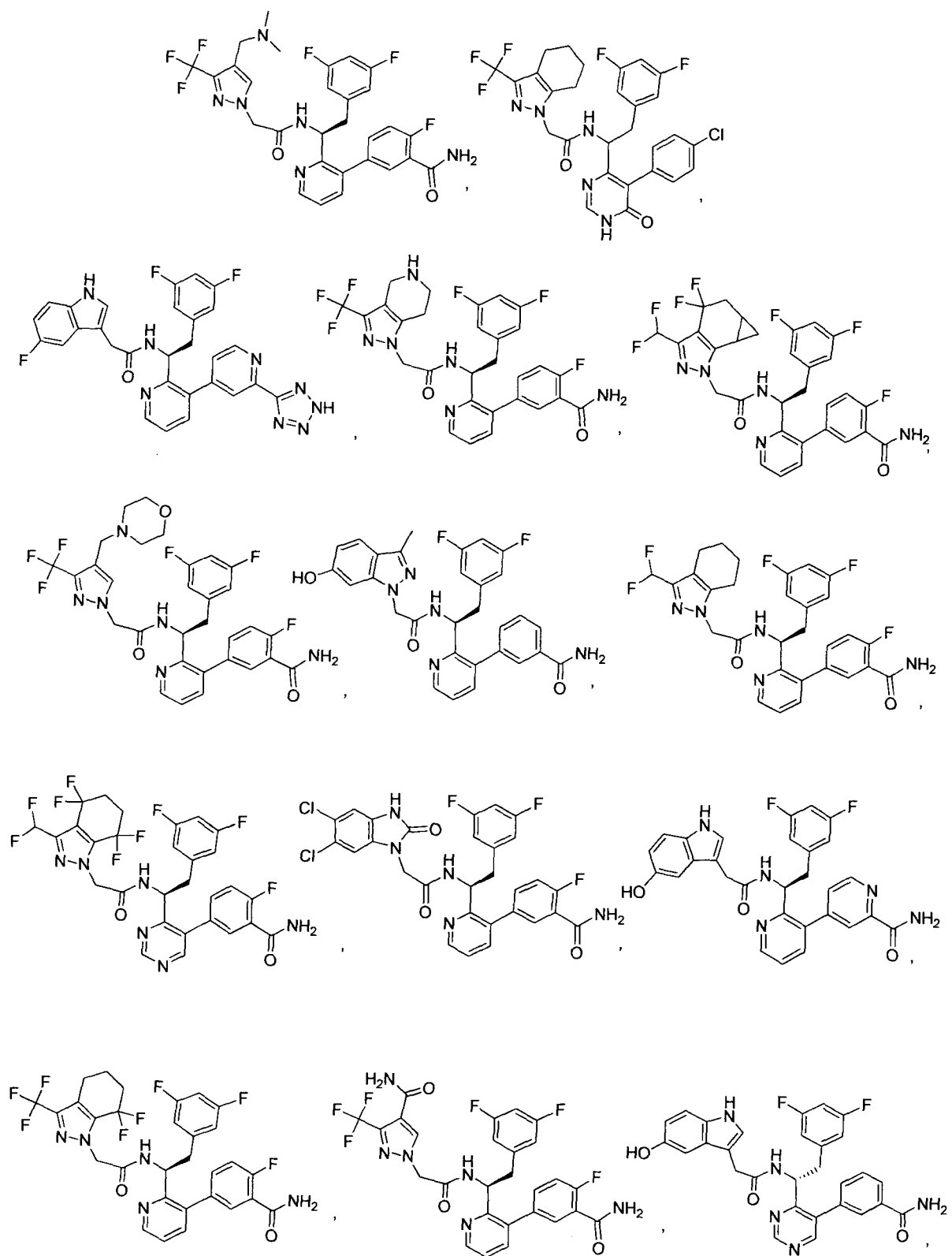


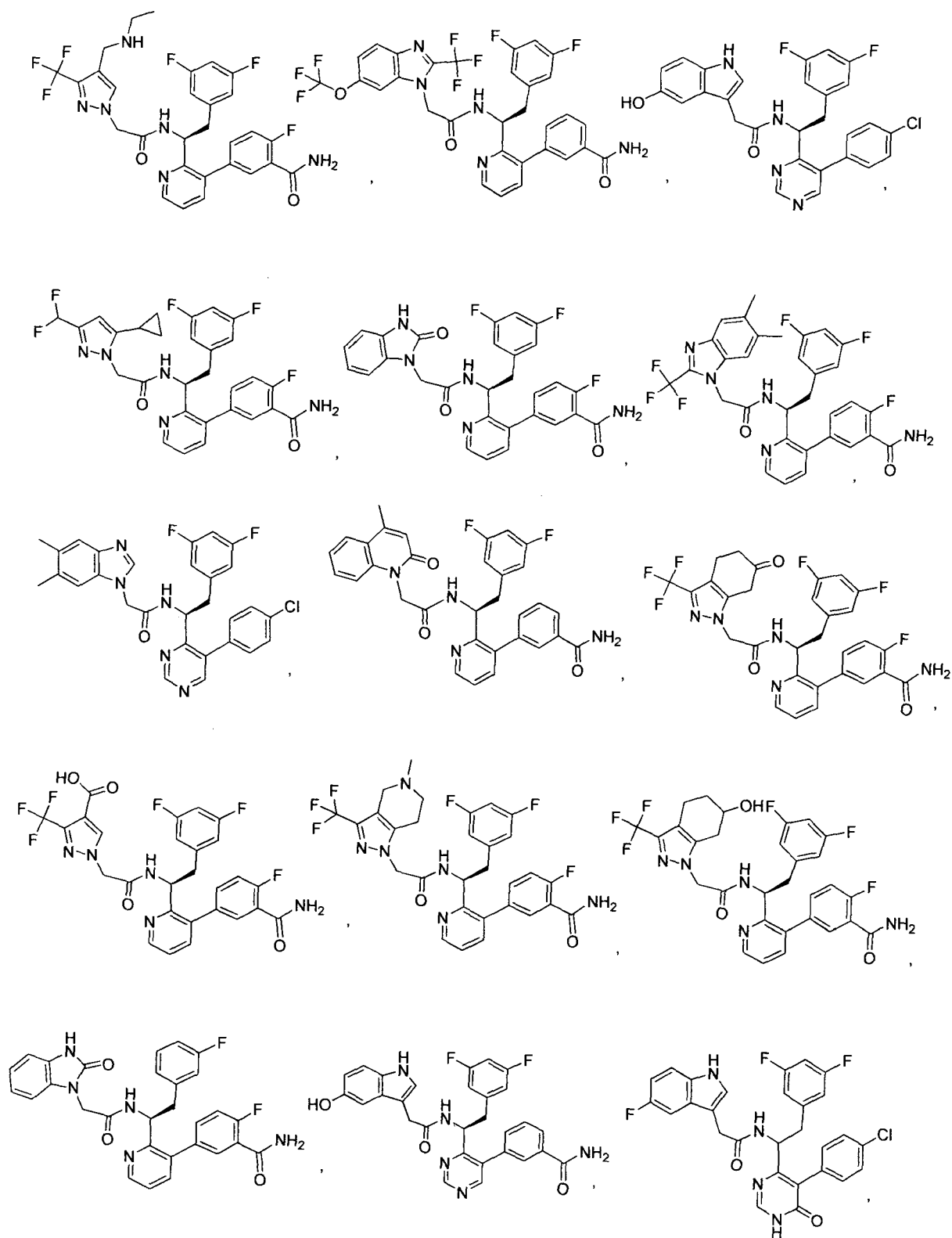


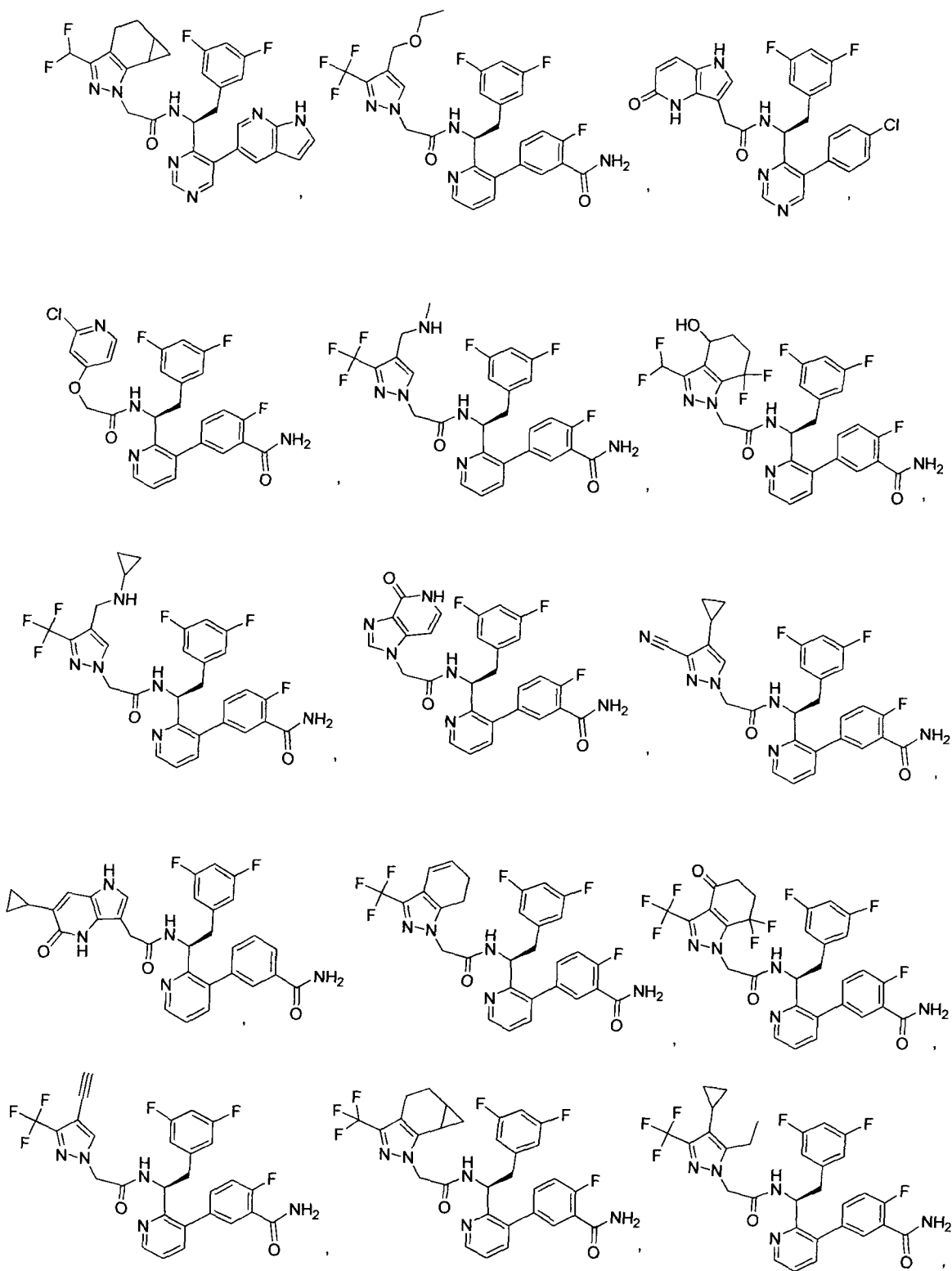


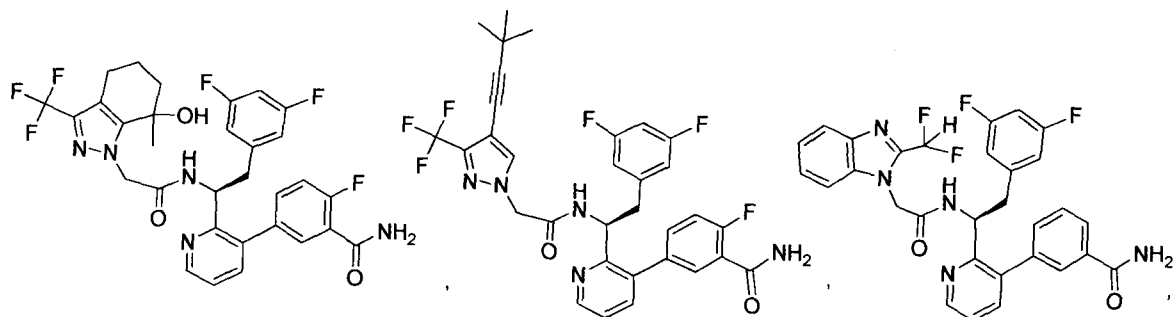
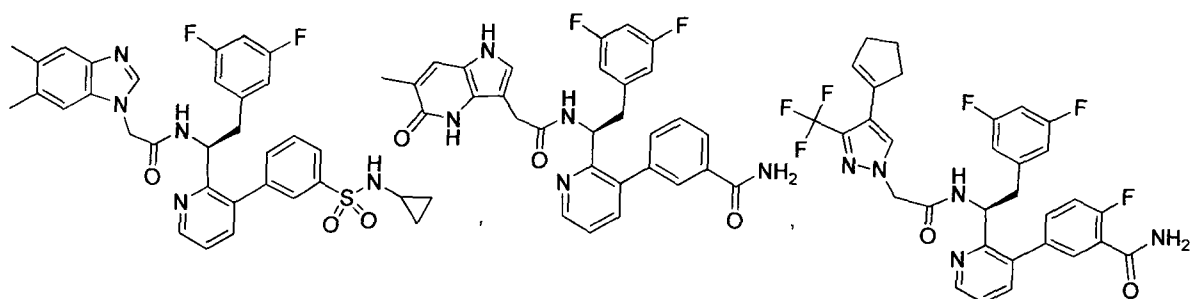
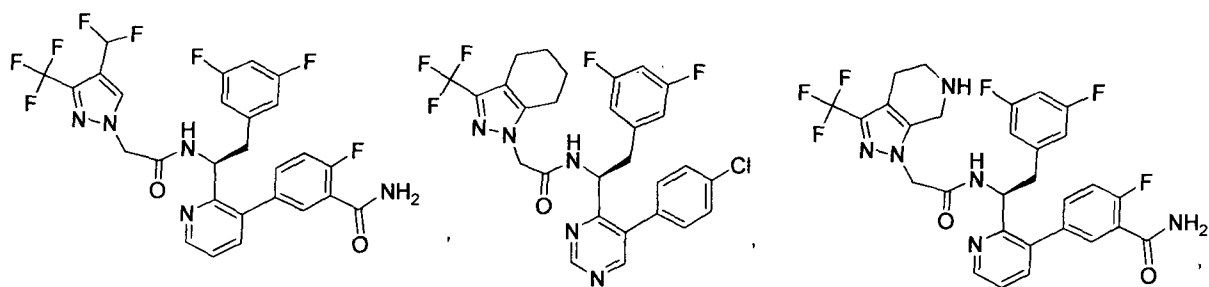
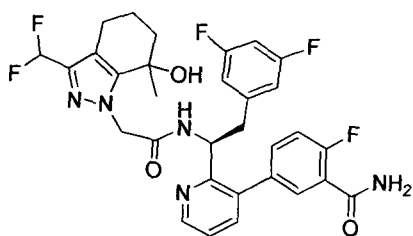
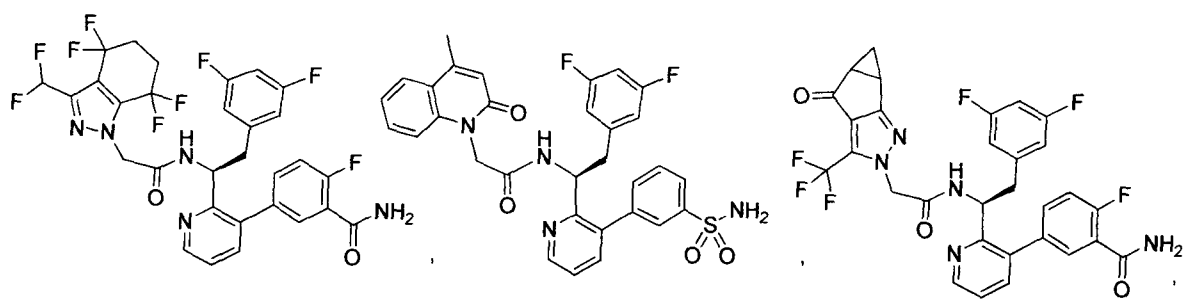


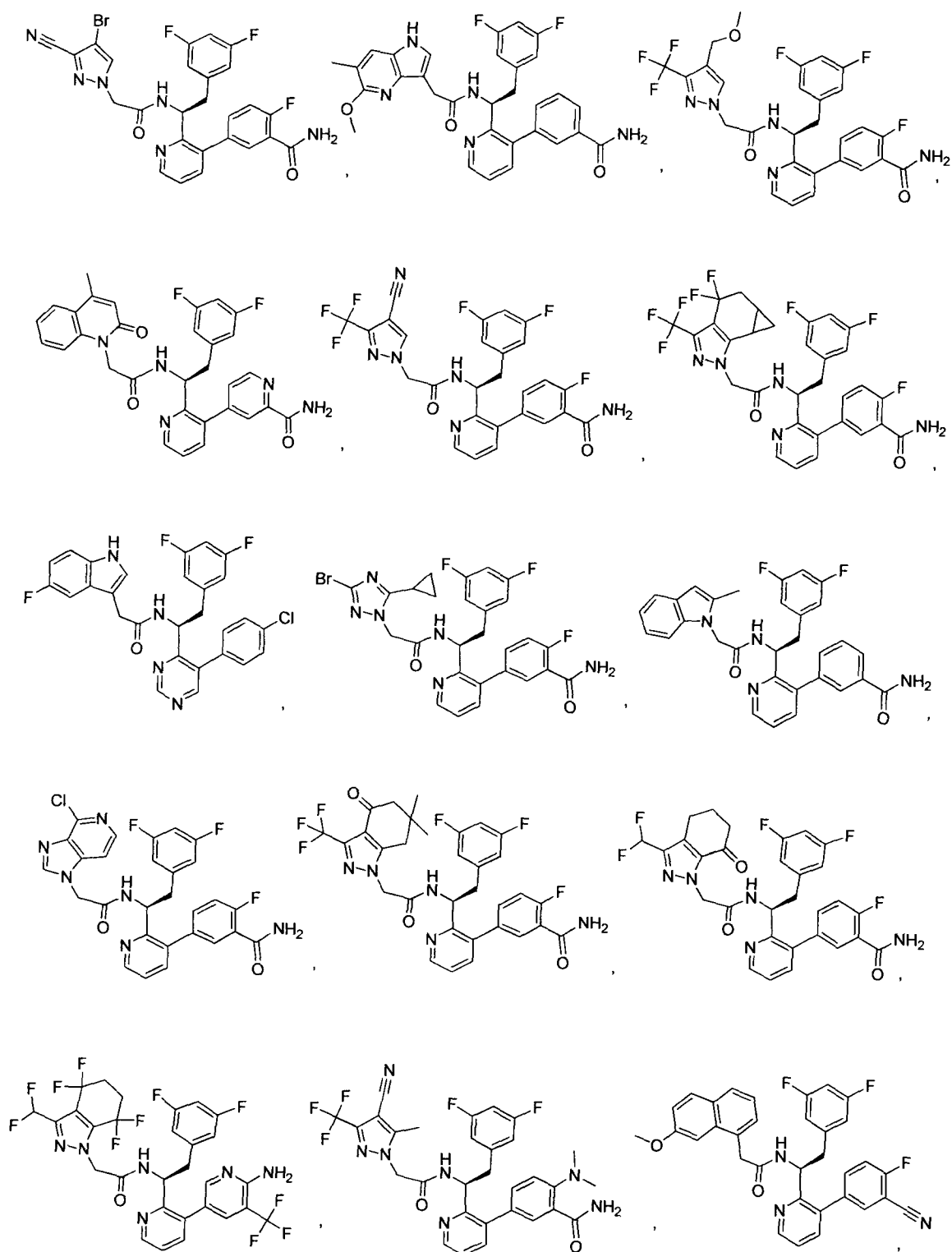


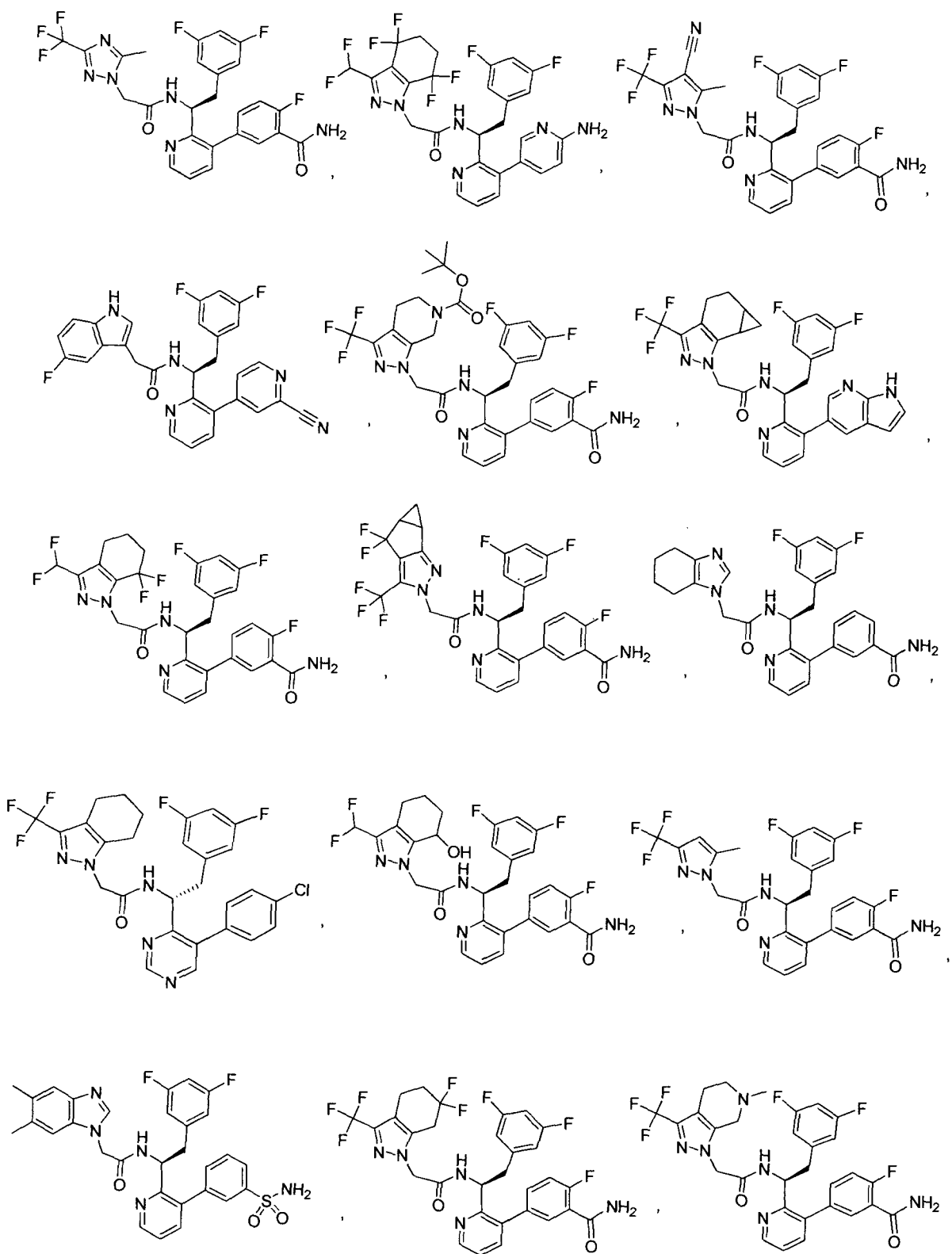


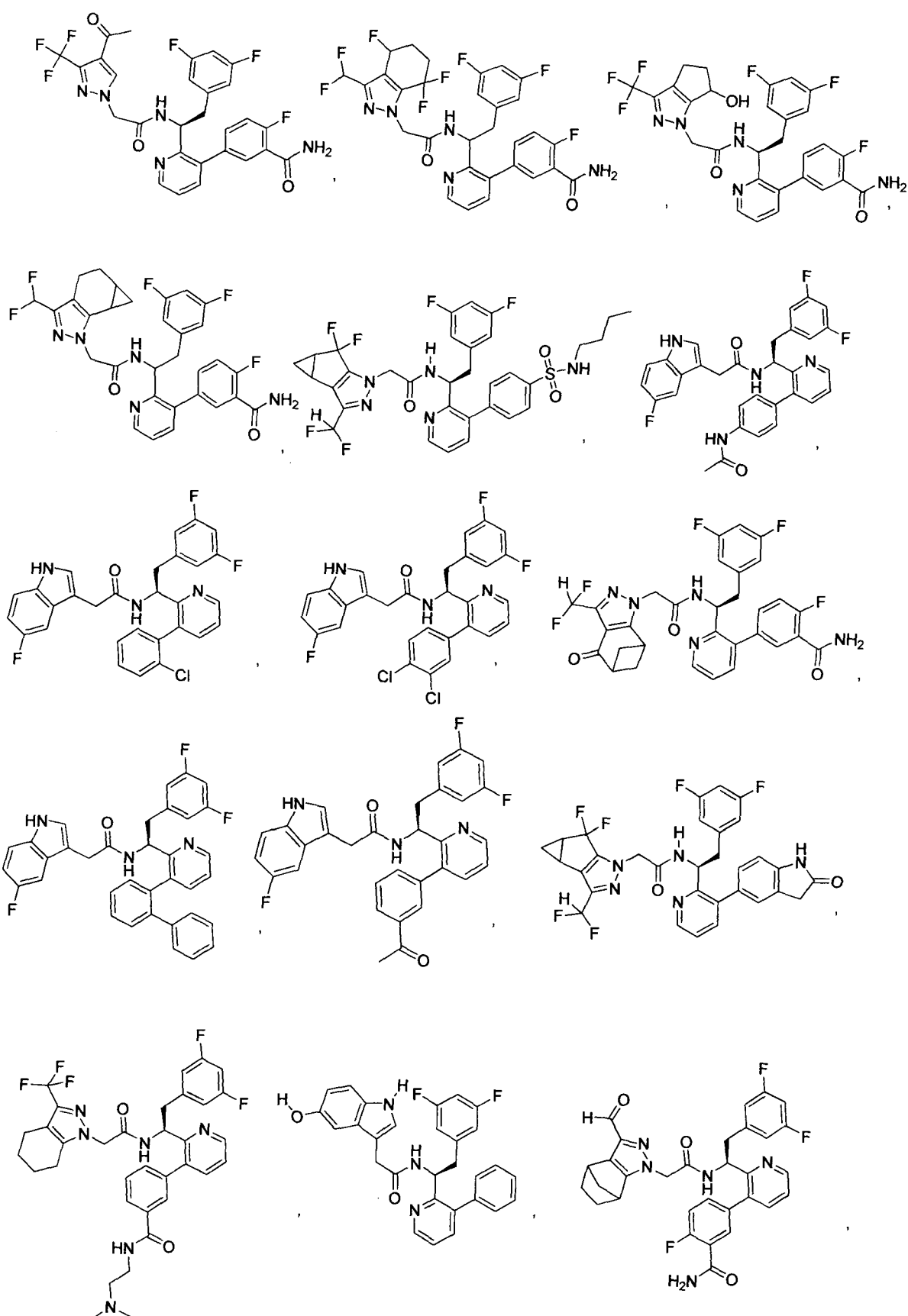


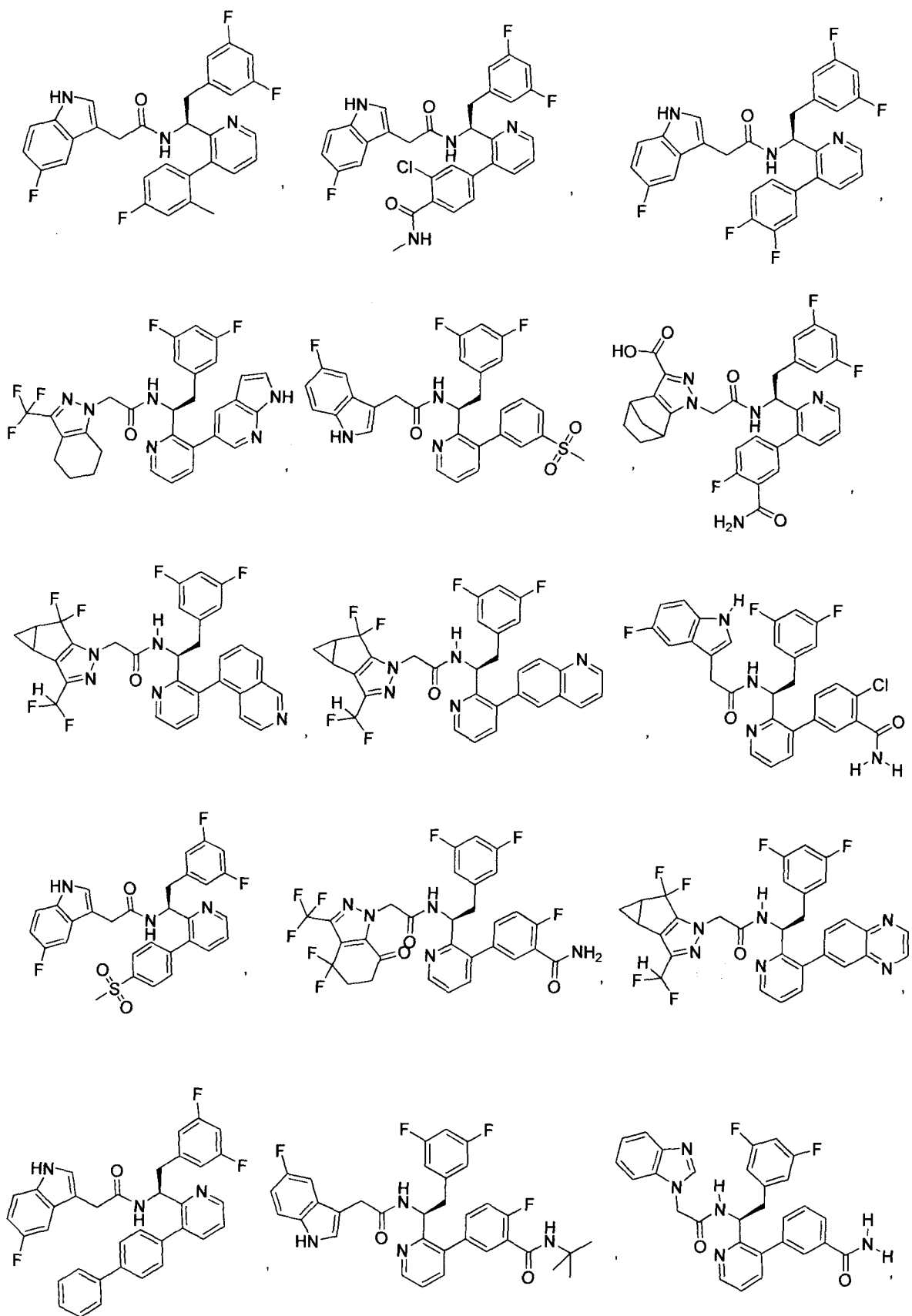


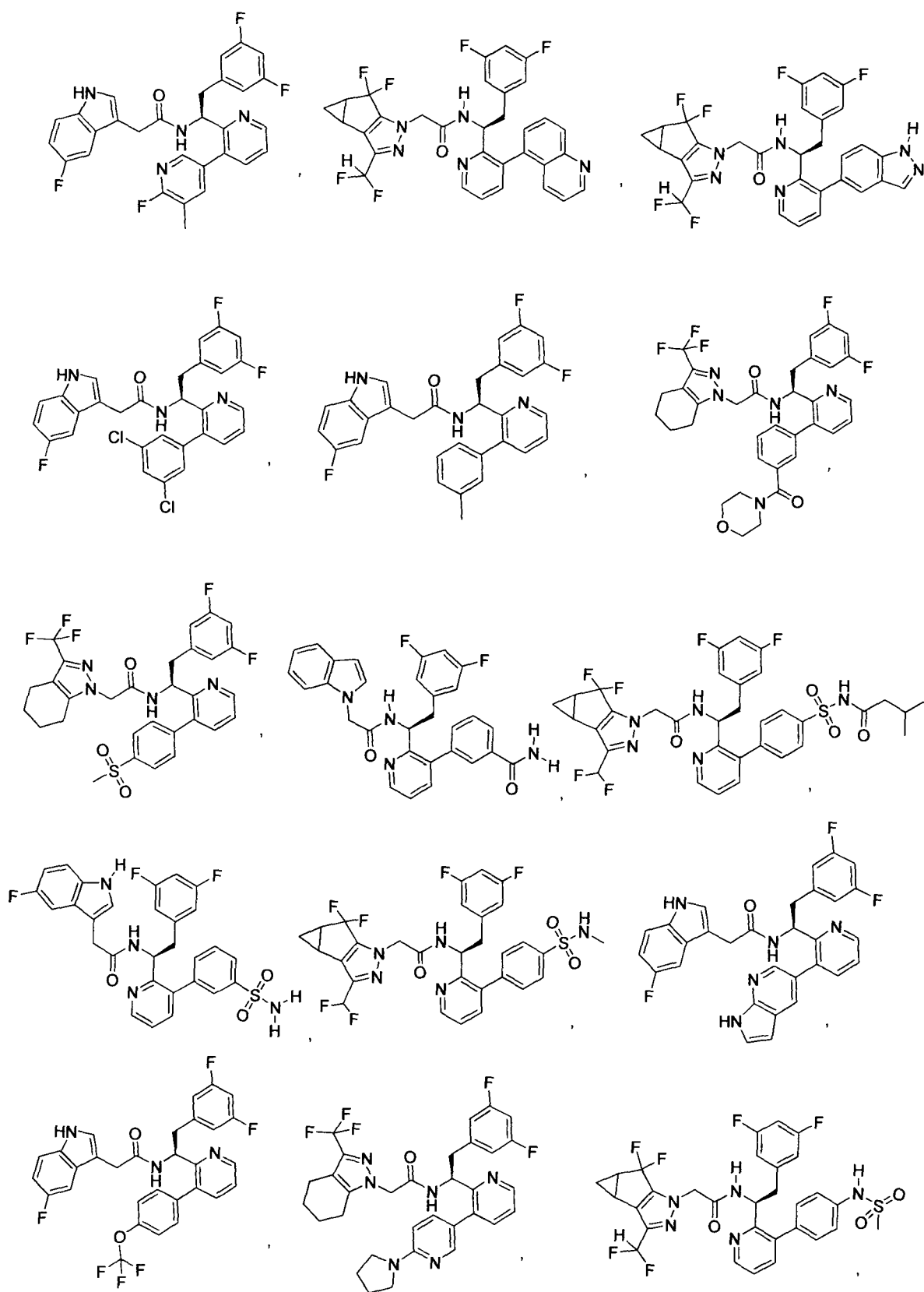


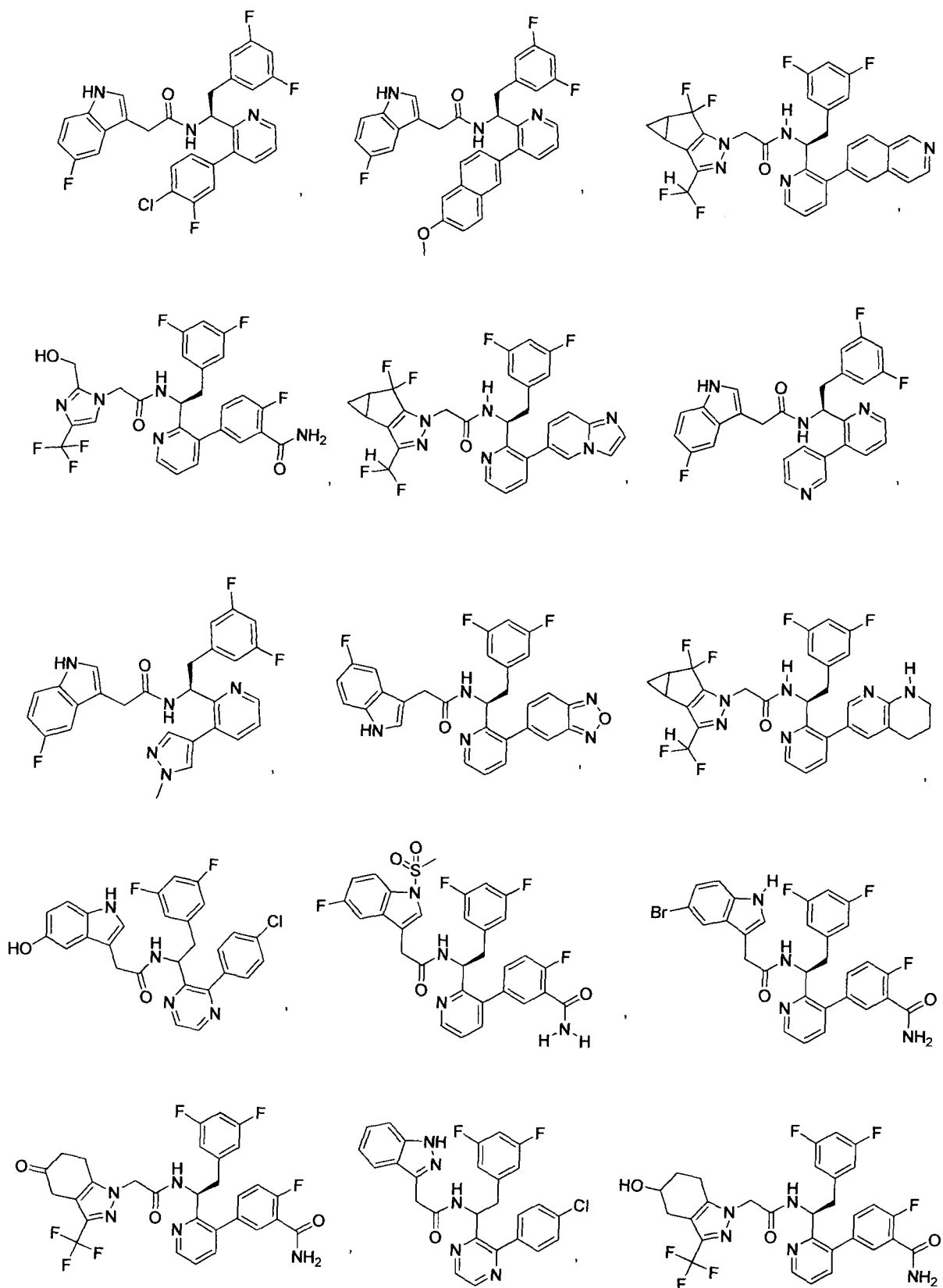


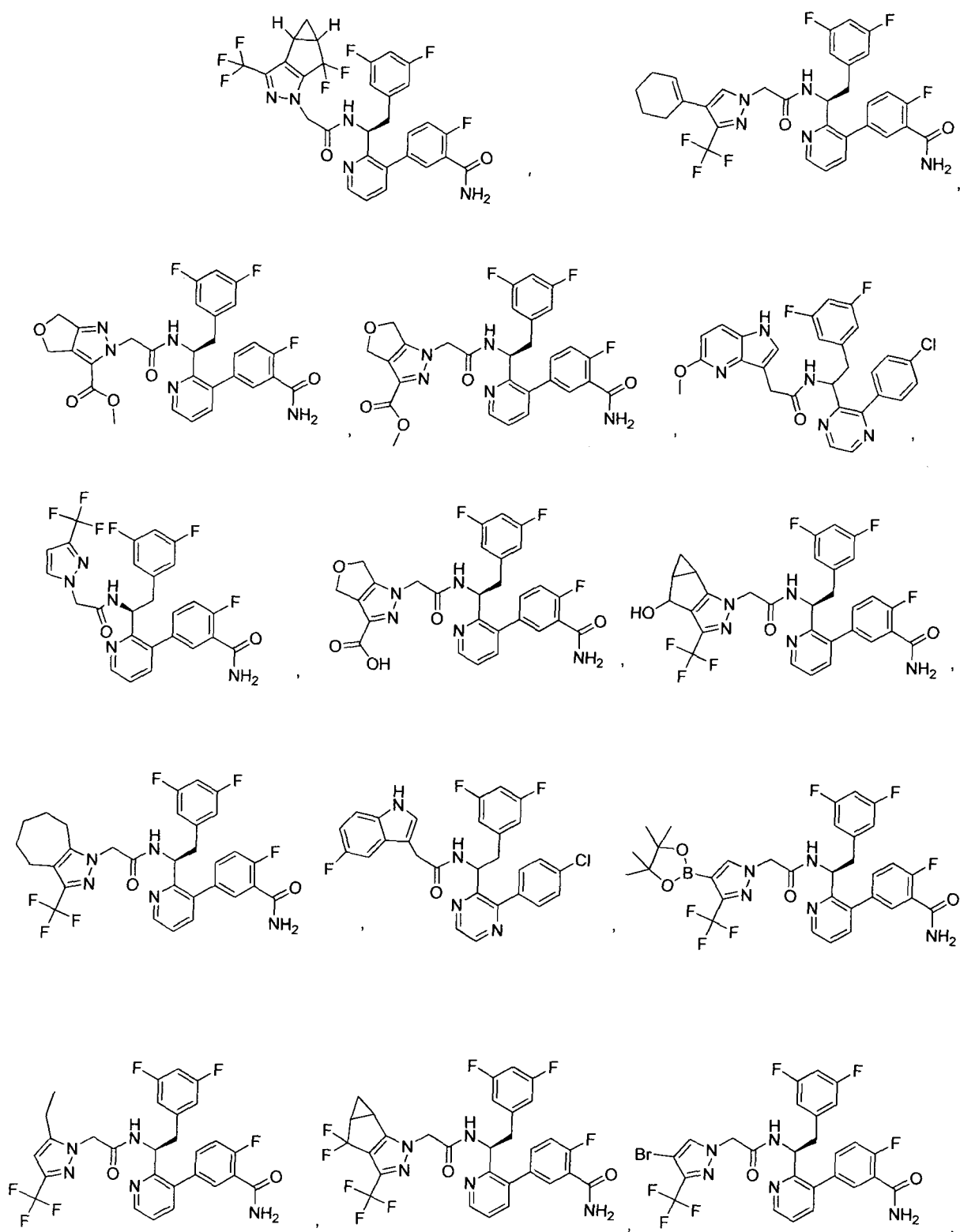


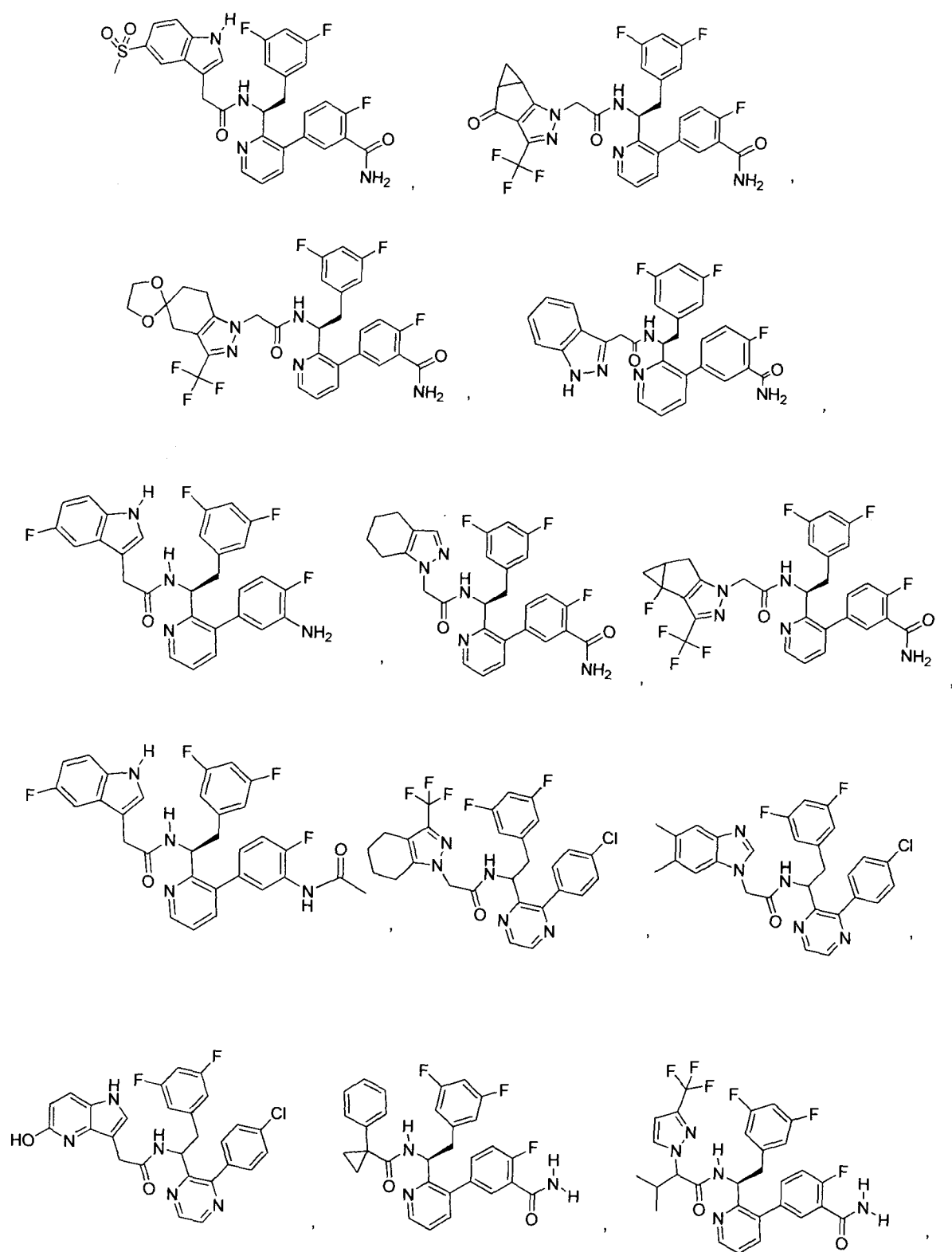


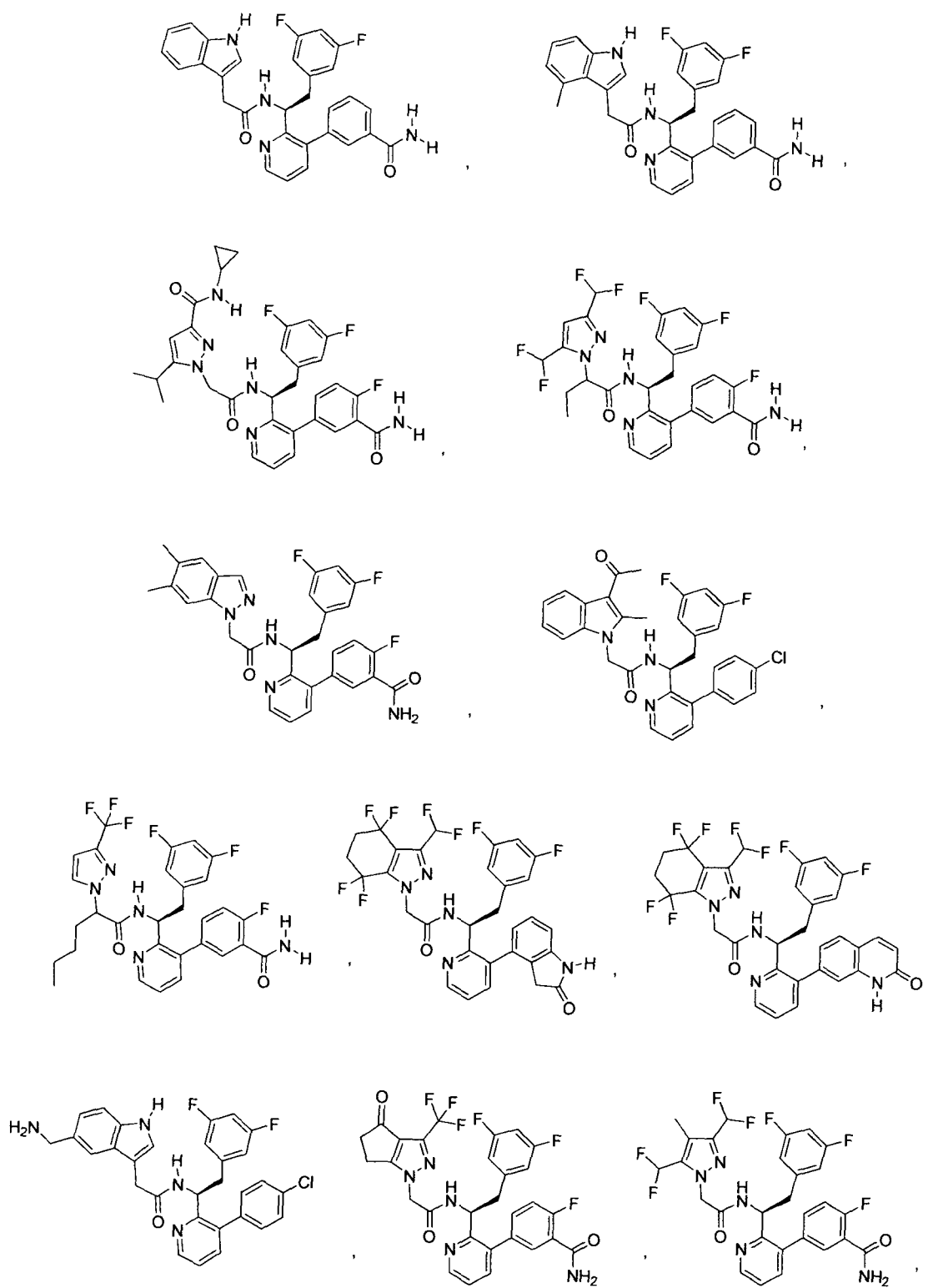


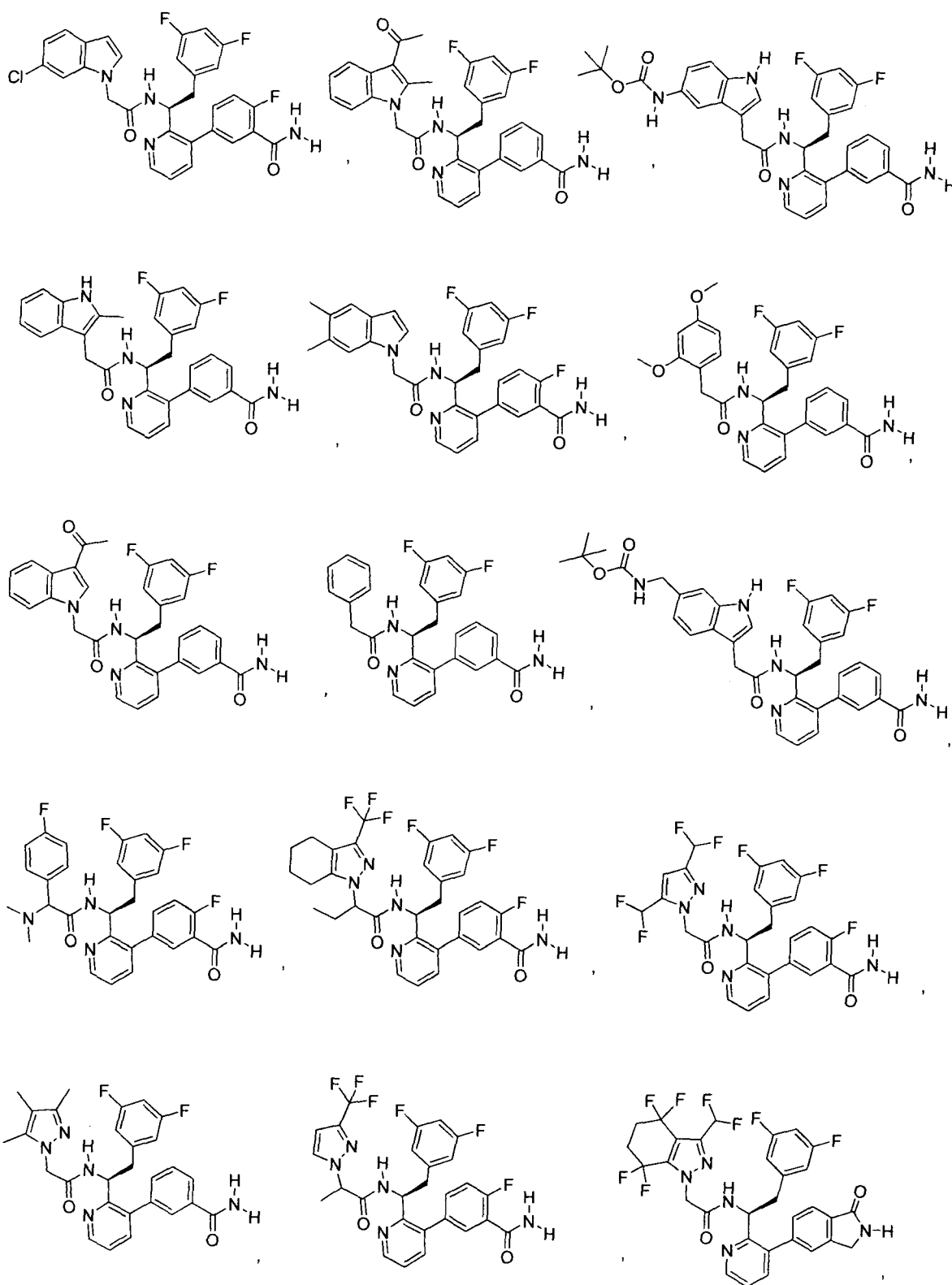


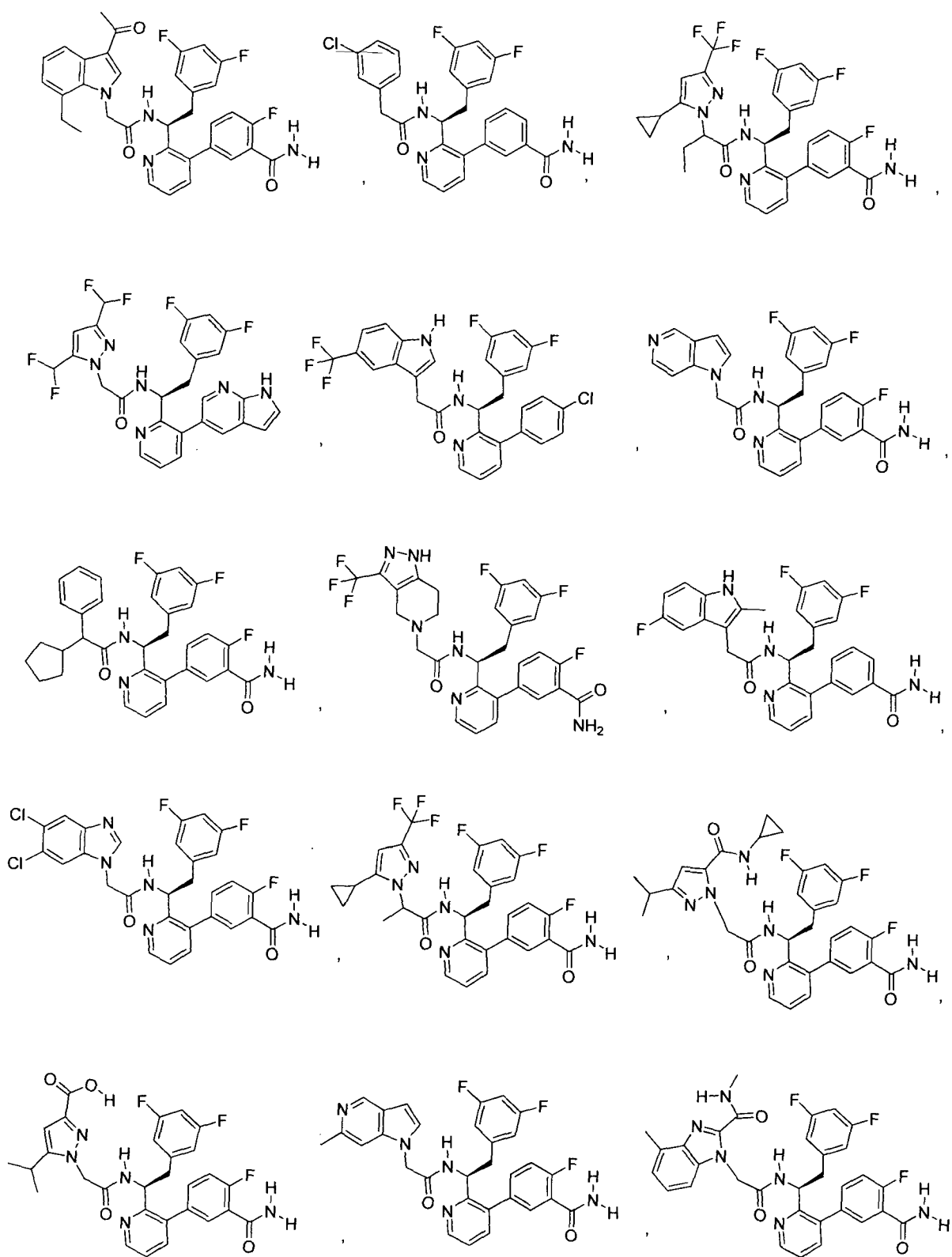


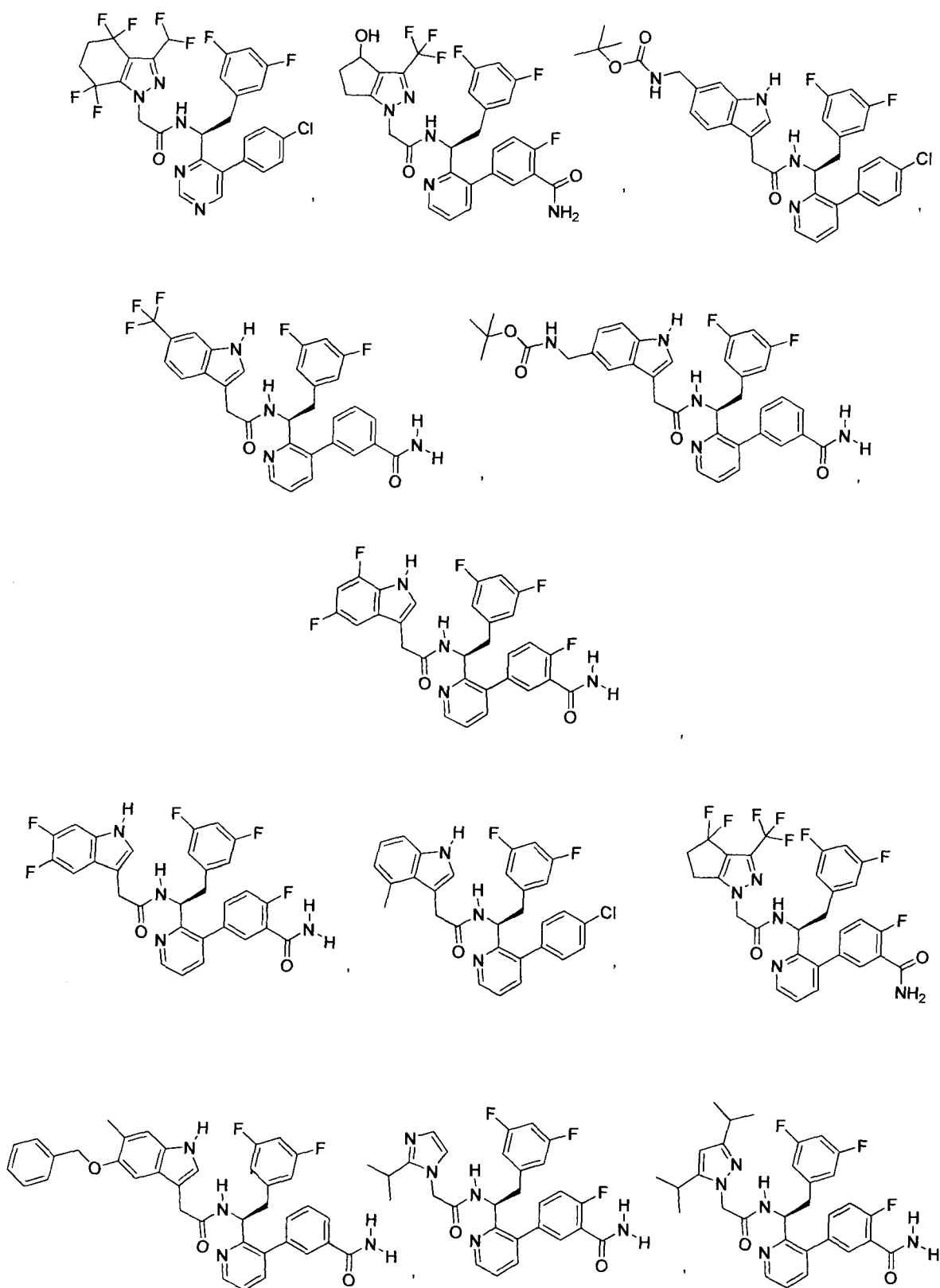


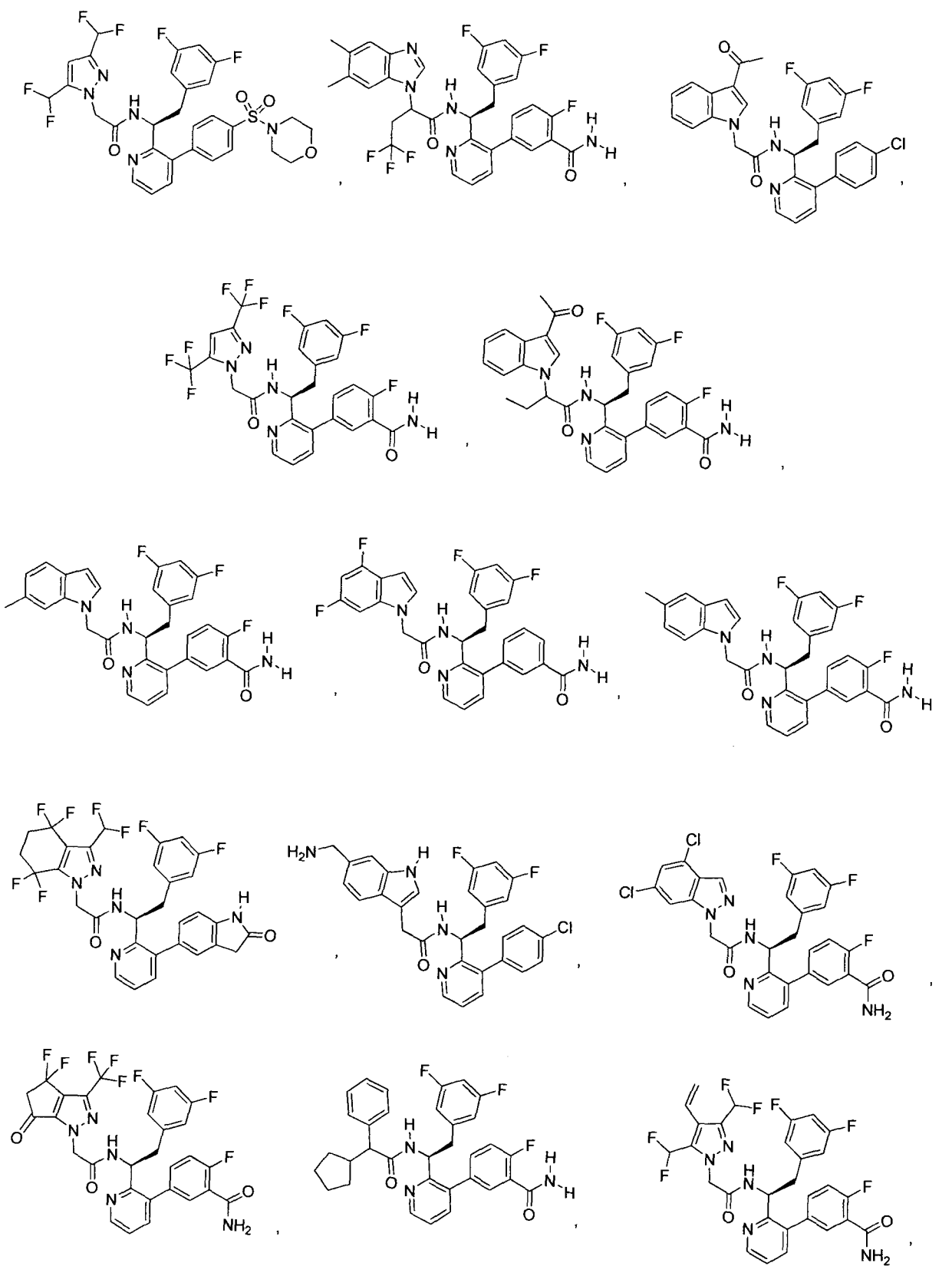


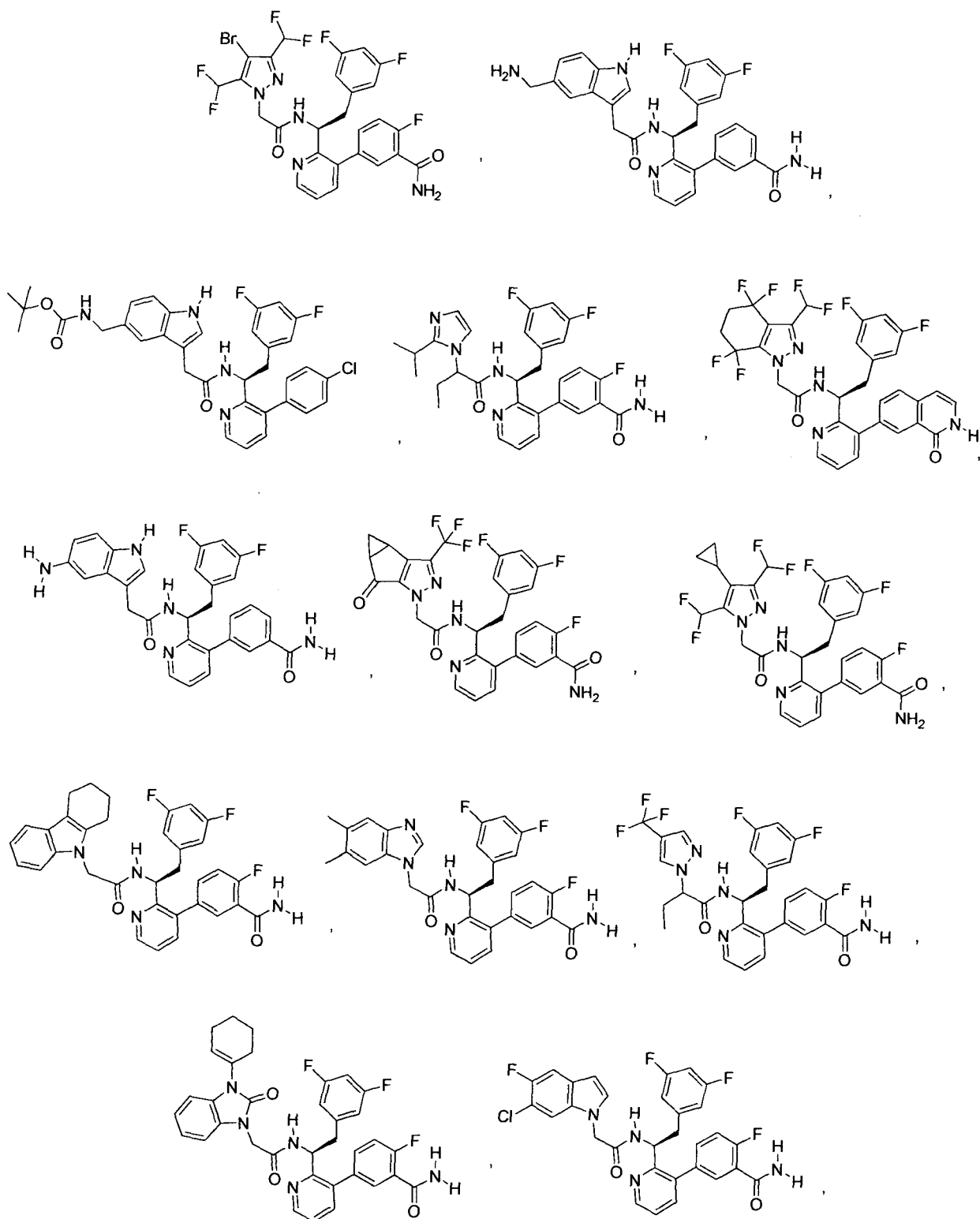


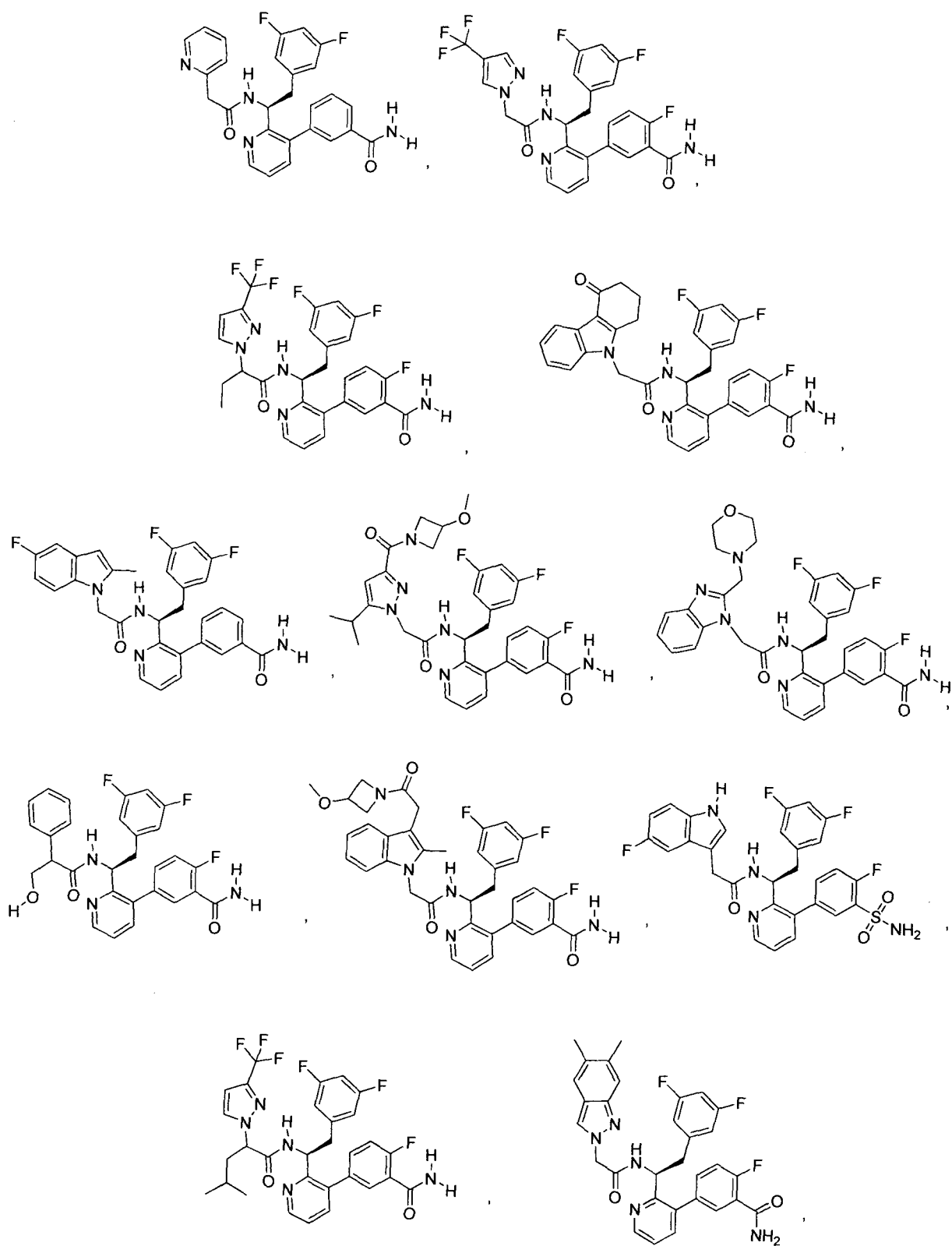


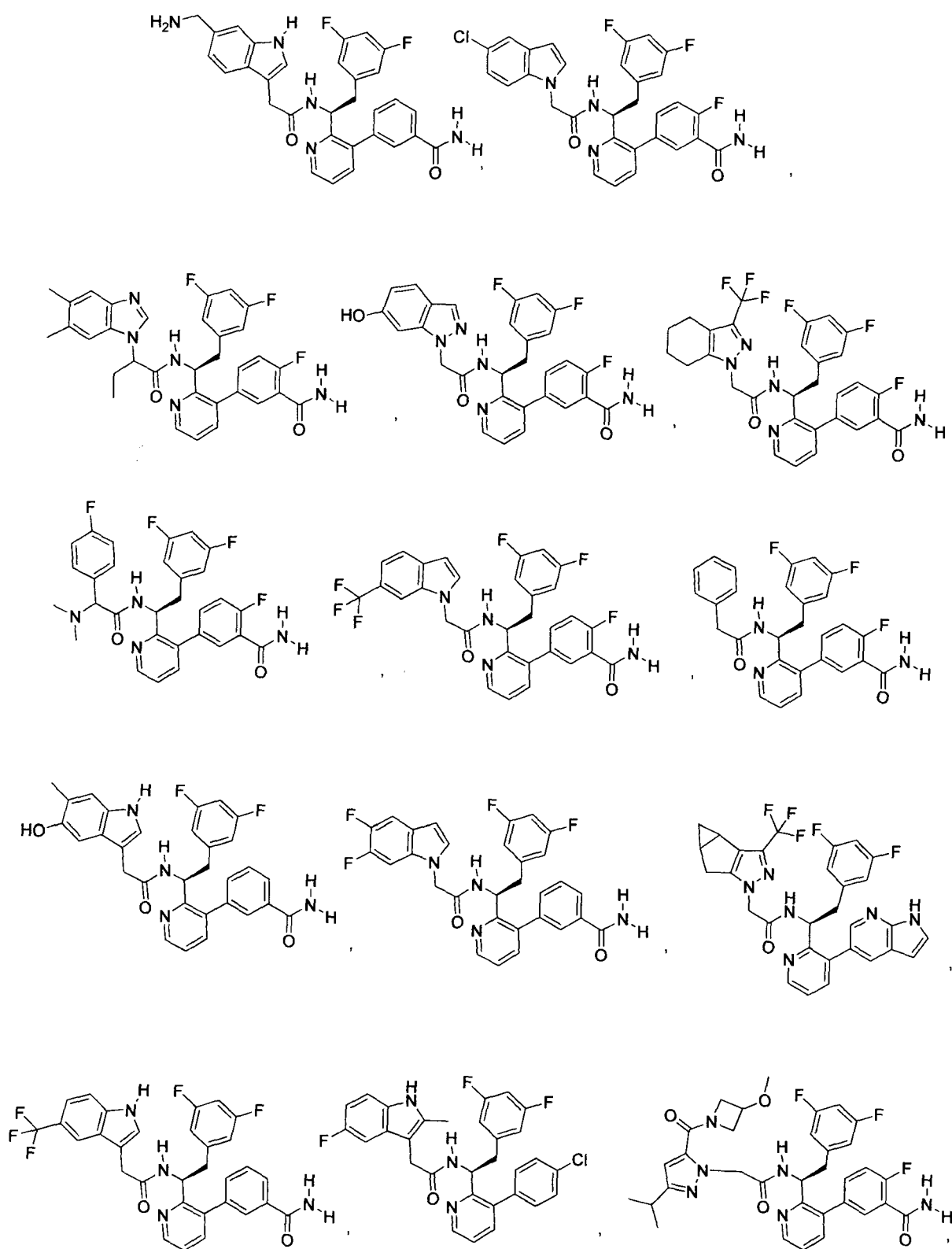


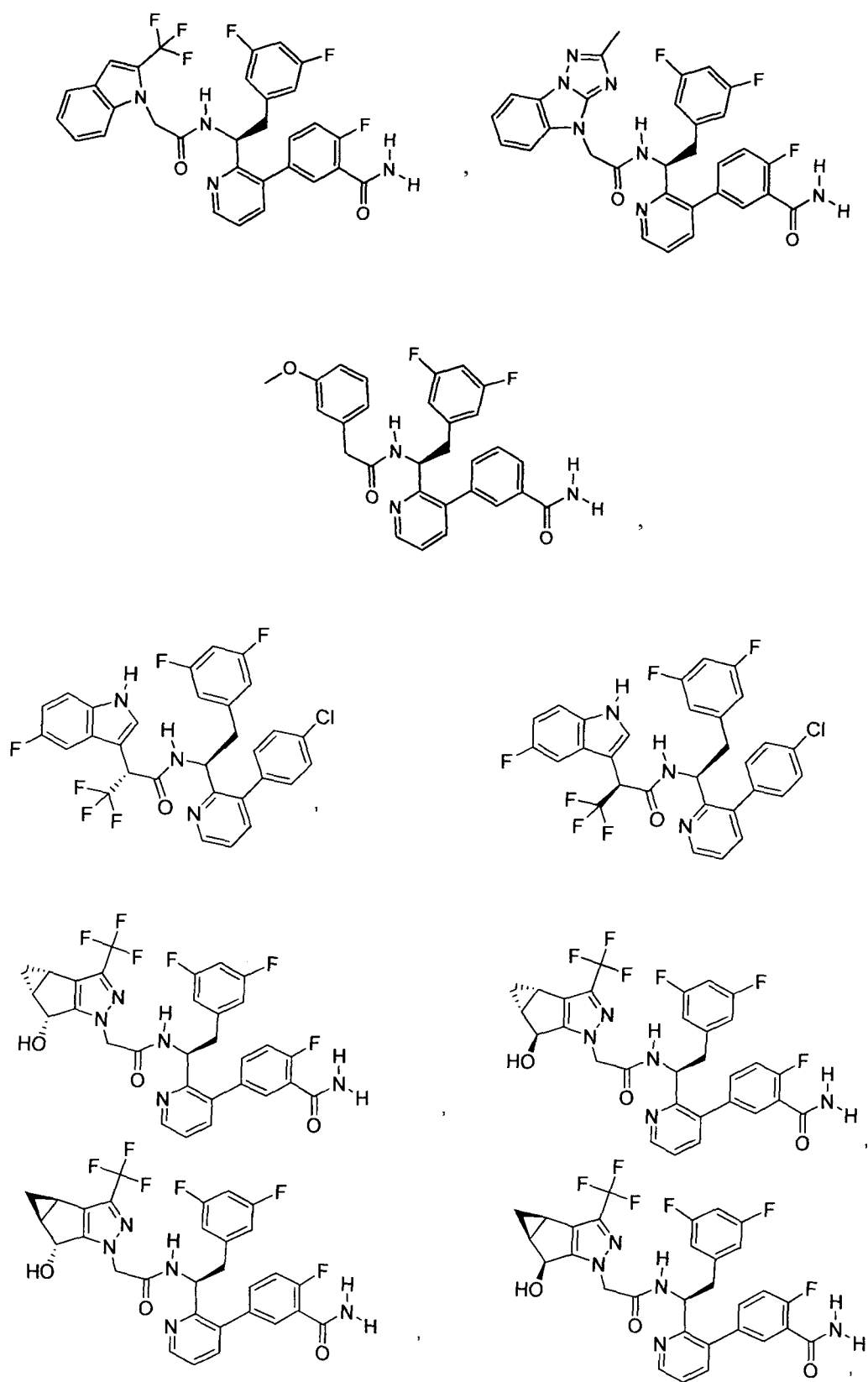


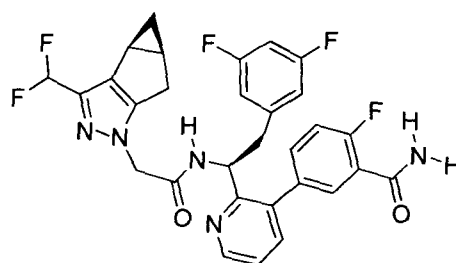
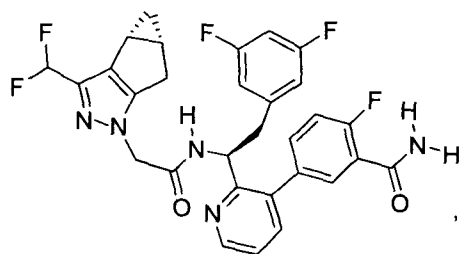
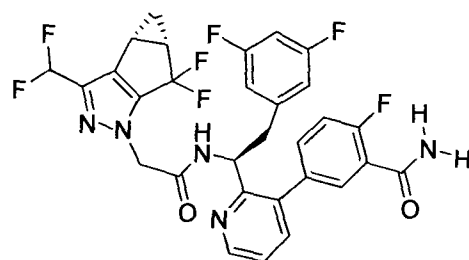
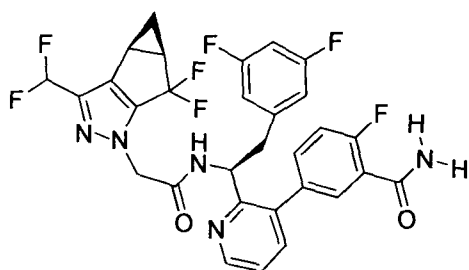
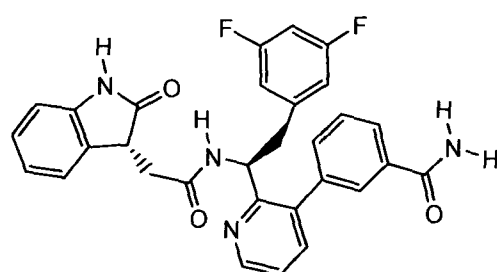
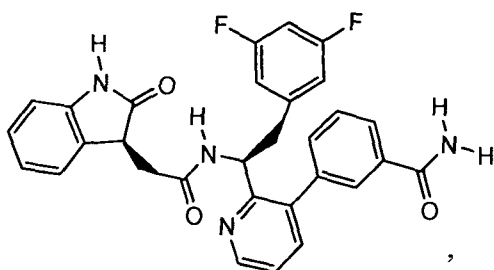
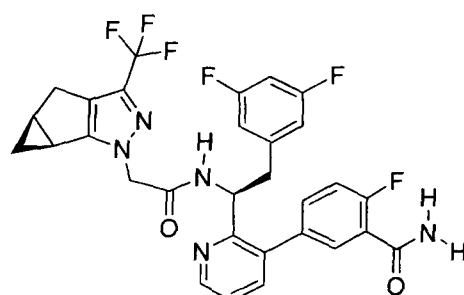
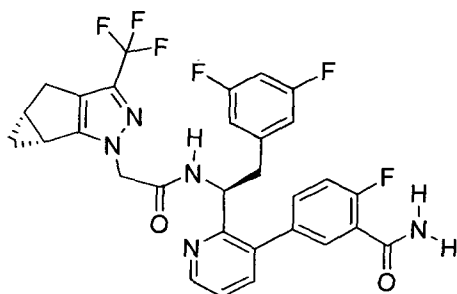
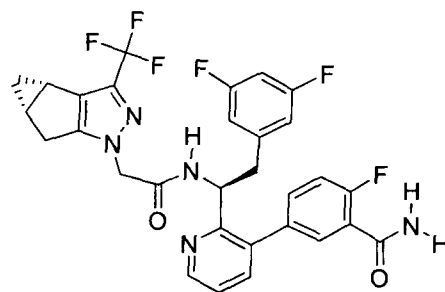
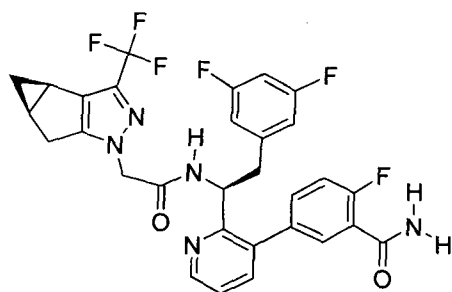


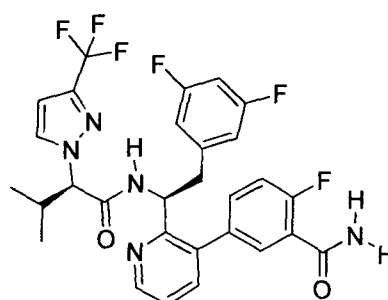
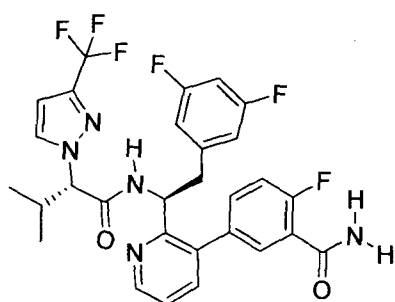
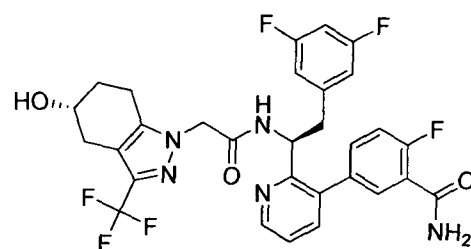
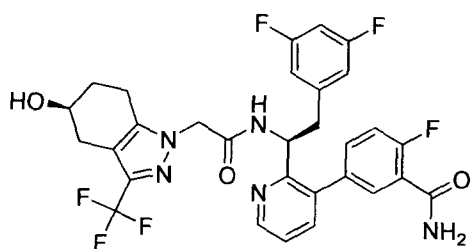
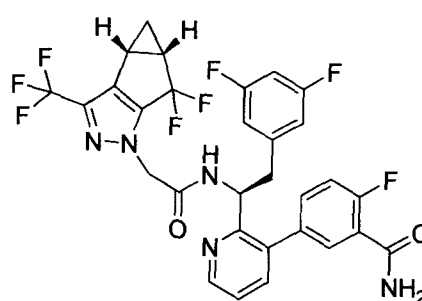
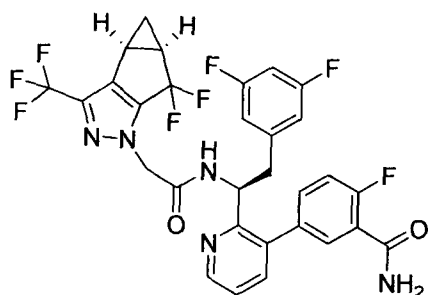
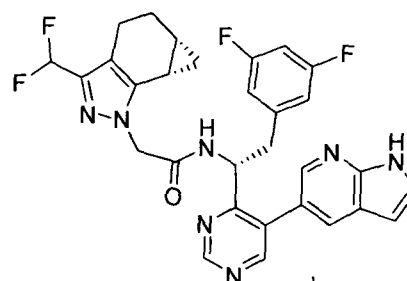
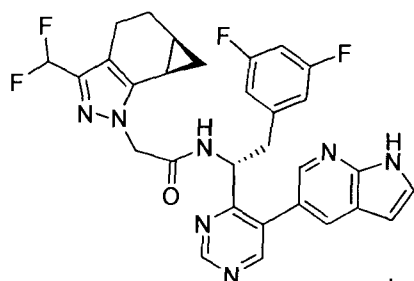
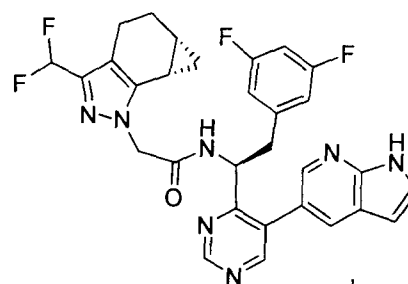
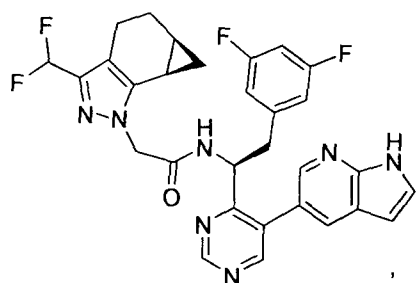


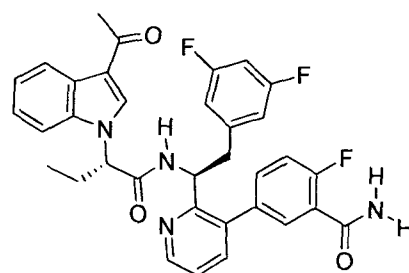
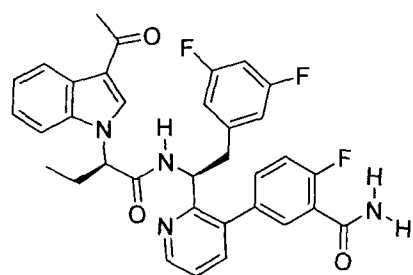
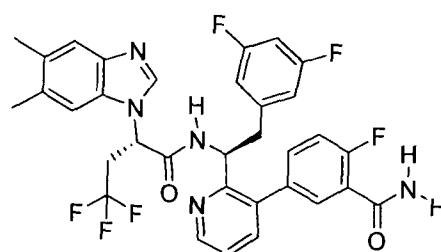
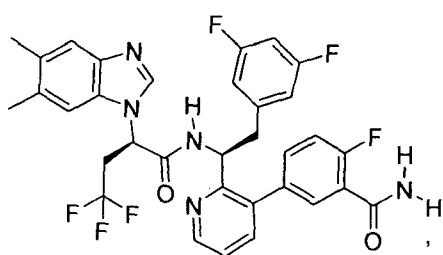
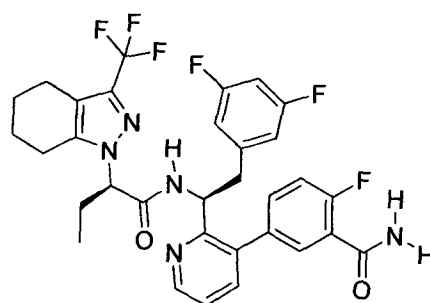
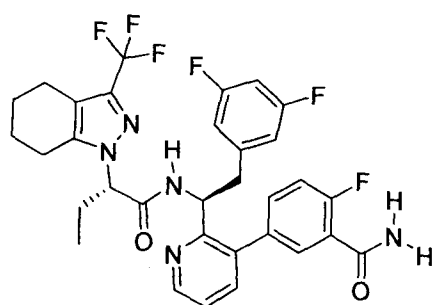
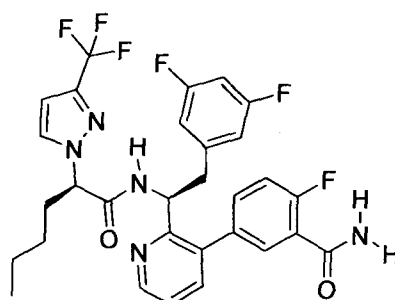
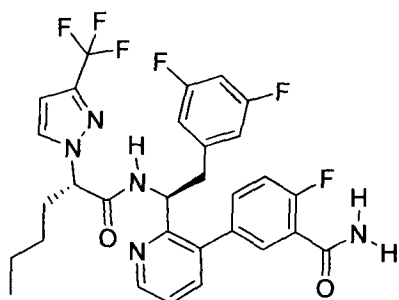
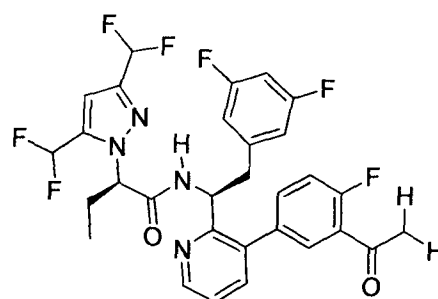
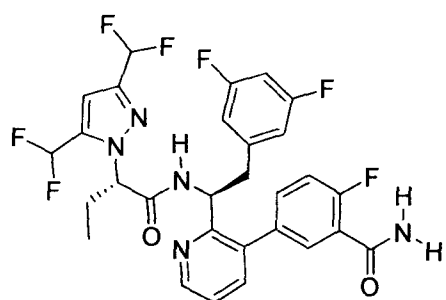


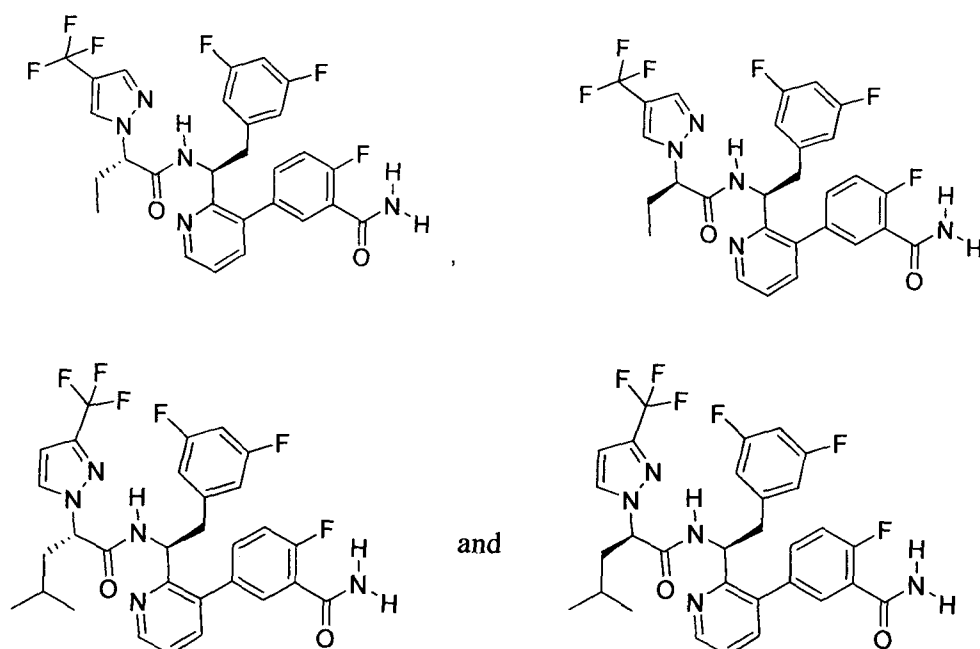






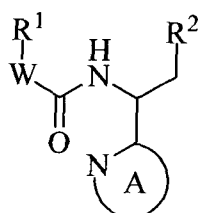






and salts thereof.

- 5 In one embodiment, the invention provides a compound of the invention which is a compound of formula I':



wherein:

- 10 A is a 6-membered heteroaryl comprising one or two nitrogens, wherein the 6-membered heteroaryl is substituted with one Z^1 group and optionally substituted with one or more (e.g. 1, 2, or 3) Z^2 groups;
- W is $CR^{3a}R^{3b}$, O or NR^4 ;
- 15 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^3 groups;
- R^2 is a 6-membered aryl, 5-membered heteroaryl or 6-membered heteroaryl, wherein any 6-membered aryl, 5-membered heteroaryl or 6-membered heteroaryl of R^2 is optionally substituted with one or more (e.g. 1, 2 or 3) Z^4 groups;
- 20 each R^{3a} and R^{3b} is independently selected from H, halogen, (C_1-C_3) alkyl, (C_1-C_3) haloalkyl, (C_1-C_6) heteroalkyl, heteroaryl (C_1-C_6) alkyl-, heterocyclyl (C_1-C_6) alkyl-,

-NR_aR_b, and -NR_cCOR_d; or R^{3a} and R^{3b} together with the carbon to which they are attached form a (C₃-C₆)carbocycle;

R⁴ is selected from H, (C₁-C₆)alkyl, (C₃-C₆)carbocycle, aryl(C₁-C₆)alkyl- and heteroaryl(C₁-C₆)alkyl-;

5 R_a and R_b are each independently selected from H, (C₁-C₈)alkyl, (C₂-C₈)alkenyl, (C₂-C₈)alkynyl, (C₃-C₇)carbocycle, heterocycle, heteroaryl, aryl, haloaryl, haloheteroaryl, haloheterocycle, (C₁-C₈)haloalkyl and (C₁-C₈)heteroalkyl, or R_a and R_b together with the nitrogen to which they are attached form a 5, 6 or 7-membered heterocycle;

10 each R_c is independently selected from H, (C₁-C₈)alkyl, (C₂-C₈)alkenyl, (C₂-C₈)alkynyl, (C₃-C₇)carbocycle, heterocycle, heteroaryl, aryl, haloaryl, haloheteroaryl, haloheterocycle, (C₁-C₈)haloalkyl and (C₁-C₈)heteroalkyl;

each R_d is independently selected from (C₁-C₈)alkyl, (C₂-C₈)alkenyl, (C₂-C₈)alkynyl, (C₃-C₇)carbocycle, heterocycle, heteroaryl, aryl, haloaryl, haloheteroaryl, haloheterocycle, (C₁-C₈)haloalkyl and (C₁-C₈)heteroalkyl;

15 each Z¹ is independently selected from (C₂-C₈)alkenyl, (C₂-C₈)alkynyl, (C₃-C₇)carbocycle, aryl, heteroaryl, heterocycle and -OR_{n1}, wherein any (C₃-C₇)carbocycle, aryl, heteroaryl and heterocycle of Z¹ is optionally substituted with one or more (e.g. 1, 2, 3, 4 or 5) Z^{1a} or Z^{1b} groups and wherein any (C₁-C₈)alkyl, (C₂-C₈)alkenyl and (C₂-C₈)alkynyl of Z¹ is optionally substituted with one or more (e.g. 1, 2, 3, 4 or 5) Z^{1a} groups;

20 each Z^{1a} is independently selected from (C₃-C₇)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)₂OH, -S(O)₂R_{p2}, -S(O)₂NR_{q2}R_{r2}, -NR_{q2}R_{r2}, -NR_{n2}COR_{p2}, -NR_{n2}CO₂R_{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}, NO₂, -C(O)R_{n2}, -C(O)OR_{n2}, and, -C(O)NR_{q2}R_{r2}, wherein any (C₃-C₇)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;

each Z^{1b} is independently selected from (C₁-C₈)alkyl, (C₂-C₈)alkenyl and (C₂-C₈)alkynyl, wherein any (C₁-C₈)alkyl, (C₂-C₈)alkenyl and (C₂-C₈)alkynyl of Z^{1b} is optionally substituted with one or more (e.g. 1, 2, 3, 4 or 5) Z^{1c} groups;

30 each Z^{1c} is independently selected from (C₃-C₇)carbocycle, aryl, heteroaryl, heterocycle, halogen, -CN, -OR_{n3}, -OC(O)R_{p3}, -OC(O)NR_{q3}R_{r3}, -SR_{n3}, -S(O)R_{p3}, -S(O)₂OH, -S(O)₂R_{p3}, -S(O)₂NR_{q3}R_{r3}, -NR_{q3}R_{r3}, -NR_{n3}COR_{p3}, -NR_{n3}CO₂R_{p3}, -NR_{n3}CONR_{q3}R_{r3}, -NR_{n3}S(O)₂R_{p3}, -NR_{n3}S(O)₂OR_{p3}, -NR_{n3}S(O)₂NR_{q3}R_{r3}, NO₂, -C(O)R_{n3}, -C(O)OR_{n3}, -C(O)NR_{q3}R_{r3}, haloaryl, haloheteroaryl, haloheterocycle and (C₁-C₈)heteroalkyl;

each Z^{1d} is independently selected from (C₁-C₈)alkyl, (C₂-C₈)alkenyl, (C₂-C₈)alkynyl and (C₁-C₈)haloalkyl;

each R_{n1} is independently selected from (C₁-C₈)alkyl, (C₂-C₈)alkenyl, (C₂-C₈)alkynyl, (C₃-C₇)carbocycle, heterocycle, heteroaryl and aryl, wherein any (C₃-C₇)carbocycle, aryl, heteroaryl and heterocycle of R_{n1} is optionally substituted with one or more (e.g. 1, 2, 3, 4 or 5) Z^{1a} or Z^{1b} groups, and wherein any (C₁-C₈)alkyl, (C₂-C₈)alkenyl and (C₂-C₈)alkynyl of R_{n1} is optionally substituted with one or more (e.g. 1, 2, 3, 4 or 5) Z^{1a} groups;

each R_{n2} is independently selected from H, (C₁-C₈)alkyl, (C₂-C₈)alkenyl, (C₂-C₈)alkynyl, (C₃-C₇)carbocycle, heterocycle, heteroaryl and aryl, wherein any (C₃-C₇)carbocycle, aryl, heteroaryl and heterocycle of R_{n2} is optionally substituted with one or more (e.g. 1, 2, 3, 4 or 5) Z^{1c} or Z^{1d} groups, and wherein any (C₁-C₈)alkyl, (C₂-C₈)alkenyl and (C₂-C₈)alkynyl of R_{n2} is optionally substituted with one or more (e.g. 1, 2, 3, 4 or 5) Z^{1c} groups;

each R_{p2} is independently selected from (C₁-C₈)alkyl, (C₂-C₈)alkenyl, (C₂-C₈)alkynyl, (C₃-C₇)carbocycle, heterocycle, heteroaryl and aryl, wherein any (C₃-C₇)carbocycle, aryl, heteroaryl and heterocycle of R_{p2} is optionally substituted with one or more (e.g. 1, 2, 3, 4 or 5) Z^{1c} or Z^{1d} groups, and wherein any (C₁-C₈)alkyl, (C₂-C₈)alkenyl and (C₂-C₈)alkynyl of R_{p2} is optionally substituted with one or more (e.g. 1, 2, 3, 4 or 5) Z^{1c} groups;

R_{q2} and R_{r2} are each independently selected from H, (C₁-C₈)alkyl, (C₂-C₈)alkenyl, (C₂-C₈)alkynyl, (C₃-C₇)carbocycle, heterocycle, heteroaryl and aryl, wherein any (C₃-C₇)carbocycle, aryl, heteroaryl and heterocycle of R_{q2} or R_{r2} is optionally substituted with one or more (e.g. 1, 2, 3, 4 or 5) Z^{1c} or Z^{1d} groups, and wherein any (C₁-C₈)alkyl, (C₂-C₈)alkenyl and (C₂-C₈)alkynyl of R_{q2} or R_{r2} is optionally substituted with one or more (e.g. 1, 2, 3, 4 or 5) Z^{1c} groups, or R_{q2} and R_{r2} 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;

each R_{n3} is independently selected from H, (C₁-C₈)alkyl, (C₂-C₈)alkenyl, (C₂-C₈)alkynyl, (C₃-C₇)carbocycle, heterocycle, heteroaryl, aryl, haloaryl, haloheteroaryl, haloheterocycle, (C₁-C₈)haloalkyl and (C₁-C₈)heteroalkyl;

each R_{p3} is independently selected from (C₁-C₈)alkyl, (C₂-C₈)alkenyl, (C₂-C₈)alkynyl, (C₃-C₇)carbocycle, heterocycle, heteroaryl, aryl, haloaryl, haloheteroaryl, haloheterocycle, (C₁-C₈)haloalkyl and (C₁-C₈)heteroalkyl;

R_{q3} and R_{r3} are each independently selected from H, (C₁-C₈)alkyl, (C₂-C₈)alkenyl, (C₂-C₈)alkynyl, (C₃-C₇)carbocycle, heterocycle, heteroaryl, aryl, haloaryl, haloheteroaryl,

haloheterocycle, (C₁-C₈)haloalkyl and (C₁-C₈)heteroalkyl, or R_{q3} and R_{r3} together with the nitrogen to which they are attached form a 5, 6 or 7-membered heterocycle;

each Z² is independently selected from (C₁-C₆)alkyl, (C₁-C₆)haloalkyl, (C₃-C₇)carbocycle, halogen, CN, OH and -O(C₁-C₆)alkyl;

5 each Z³ is independently selected from (C₁-C₈)alkyl, (C₂-C₈)alkenyl, (C₂-C₈)alkynyl, (C₃-C₇)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)₂OH, -S(O)₂R_{p4}, -S(O)₂NR_{q4}R_{r4}, -NR_{q4}R_{r4}, -NR_{n4}COR_{p4}, -NR_{n4}CO₂R_{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}, NO₂, -C(O)R_{n4}, -C(O)OR_{n4}, and -C(O)NR_{q4}R_{r4}, wherein any (C₃-C₇)carbocycle, aryl, heteroaryl and
10 heterocycle of Z³ is optionally substituted with one or more (e.g. 1, 2, 3, 4 or 5) Z^{3a} or Z^{3b} groups, and wherein any (C₁-C₈)alkyl, (C₂-C₈)alkenyl and (C₂-C₈)alkynyl of Z³ is optionally substituted with one or more (e.g. 1, 2, 3, 4 or 5) Z^{3a} groups;

each Z^{3a} is independently selected from (C₃-C₇)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)₂OH, -S(O)₂R_{p5},
15 -S(O)₂NR_{q5}R_{r5}, -NR_{q5}R_{r5}, -NR_{n5}COR_{p5}, -NR_{n5}CO₂R_{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}, NO₂, -C(O)R_{n5}, -C(O)OR_{n5}, and -C(O)NR_{q5}R_{r5}, wherein any (C₃-C₇)carbocycle, aryl, heteroaryl and heterocycle of Z^{3a} is optionally substituted with one or more (e.g. 1, 2, 3, 4 or 5) Z^{3c} or Z^{3d} groups;

each Z^{3b} is independently selected from (C₁-C₈)alkyl, (C₂-C₈)alkenyl and (C₂-C₈)alkynyl,
20 wherein any (C₁-C₈)alkyl, (C₂-C₈)alkenyl and (C₂-C₈)alkynyl of Z^{3b} is optionally substituted with one or more (e.g. 1, 2, 3, 4 or 5) Z^{3c} groups;

each Z^{3c} is independently selected from (C₃-C₇)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)₂OH, -S(O)₂R_{p6},
25 -S(O)₂NR_{q6}R_{r6}, -NR_{q6}R_{r6}, -NR_{n6}COR_{p6}, -NR_{n6}CO₂R_{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}, NO₂, -C(O)R_{n6}, -C(O)OR_{n6}, -C(O)NR_{q6}R_{r6}, haloaryl, haloheteroaryl, haloheterocycle and (C₁-C₈)heteroalkyl;

each Z^{3d} is independently selected from (C₁-C₈)alkyl, (C₂-C₈)alkenyl, (C₂-C₈)alkynyl, and (C₁-C₈)haloalkyl;

each R_{n4} is independently selected from H, (C₁-C₈)alkyl, (C₂-C₈)alkenyl, (C₂-C₈)alkynyl, (C₃-C₇)carbocycle, heterocycle, heteroaryl and aryl, wherein any (C₃-C₇)carbocycle, aryl,
30 heteroaryl and heterocycle of R_{n4} is optionally substituted with one or more (e.g. 1, 2, 3, 4 or 5) Z^{3a} or Z^{3b} groups, and wherein any (C₁-C₈)alkyl, (C₂-C₈)alkenyl and (C₂-C₈)alkynyl of R_{n4} is optionally substituted with one or more (e.g. 1, 2, 3, 4 or 5) Z^{3a} groups;

each R_{p4} is independently selected from (C₁-C₈)alkyl, (C₂-C₈)alkenyl, (C₂-C₈)alkynyl, (C₃-C₇)carbocycle, heterocycle, heteroaryl and aryl, wherein any (C₃-C₇)carbocycle, aryl, heteroaryl, or heterocycle of R_{p4} is optionally substituted with one or more (e.g. 1, 2, 3, 4 or 5) Z^{3a} or Z^{3b} groups, and wherein any (C₁-C₈)alkyl, (C₂-C₈)alkenyl or (C₂-C₈)alkynyl of R_{p4} is optionally substituted with one or more (e.g. 1, 2, 3, 4 or 5) Z^{3a} groups;

R_{q4} and R_{r4} are each independently selected from H, (C₁-C₈)alkyl, (C₂-C₈)alkenyl, (C₂-C₈)alkynyl, (C₃-C₇)carbocycle, heterocycle, heteroaryl and aryl, wherein any (C₃-C₇)carbocycle, aryl, heteroaryl and heterocycle of R_{q4} or R_{r4} is optionally substituted with one or more (e.g. 1, 2, 3, 4 or 5) Z^{3a} or Z^{3b} groups, and wherein any (C₁-C₈)alkyl, (C₂-C₈)alkenyl and (C₂-C₈)alkynyl of R_{q4} or R_{r4} is optionally substituted with one or more (e.g. 1, 2, 3, 4 or 5) Z^{3a} groups, or R_{q4} and R_{r4} 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^{3a} or Z^{3b} groups;

each R_{n5} is independently selected from H, (C₁-C₈)alkyl, (C₂-C₈)alkenyl, (C₂-C₈)alkynyl, (C₃-C₇)carbocycle, heterocycle, heteroaryl and aryl, wherein any (C₃-C₇)carbocycle, aryl, heteroaryl and heterocycle of R_{n5} is optionally substituted with one or more (e.g. 1, 2, 3, 4 or 5) Z^{3c} or Z^{3d} groups, and wherein any (C₁-C₈)alkyl, (C₂-C₈)alkenyl and (C₂-C₈)alkynyl of R_{n5} is optionally substituted with one or more (e.g. 1, 2, 3, 4 or 5) Z^{3c} groups;

each R_{p5} is independently selected from (C₁-C₈)alkyl, (C₂-C₈)alkenyl, (C₂-C₈)alkynyl, (C₃-C₇)carbocycle, heterocycle, heteroaryl and aryl, wherein any (C₃-C₇)carbocycle, aryl, heteroaryl and heterocycle of R_{p5} is optionally substituted with one or more (e.g. 1, 2, 3, 4 or 5) Z^{3c} or Z^{3d} groups, and wherein any (C₁-C₈)alkyl, (C₂-C₈)alkenyl and (C₂-C₈)alkynyl of R_{p5} is optionally substituted with one or more (e.g. 1, 2, 3, 4 or 5) Z^{3c} groups;

R_{q5} and R_{r5} are each independently selected from H, (C₁-C₈)alkyl, (C₂-C₈)alkenyl, (C₂-C₈)alkynyl, (C₃-C₇)carbocycle, heterocycle, heteroaryl and aryl, wherein any (C₃-C₇)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^{3c} or Z^{3d} groups, and wherein any (C₁-C₈)alkyl, (C₂-C₈)alkenyl and (C₂-C₈)alkynyl of R_{q5} or R_{r5} is optionally substituted with one or more (e.g. 1, 2, 3, 4 or 5) Z^{3c} 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^{3c} or Z^{3d} groups;

each R_{n6} is independently selected from H, (C₁-C₈)alkyl, (C₂-C₈)alkenyl, (C₂-C₈)alkynyl, (C₃-C₇)carbocycle, heterocycle, heteroaryl, aryl, haloaryl, haloheteroaryl, haloheterocycle, (C₁-C₈)haloalkyl and (C₁-C₈)heteroalkyl;

each R_{p6} is independently selected from (C₁-C₈)alkyl, (C₂-C₈)alkenyl, (C₂-C₈)alkynyl, (C₃-C₇)carbocycle, heterocycle, heteroaryl, aryl, haloaryl, haloheteroaryl, haloheterocycle, (C₁-C₈)haloalkyl and (C₁-C₈)heteroalkyl;

R_{q6} and R_{r6} are each independently selected from H, (C₁-C₈)alkyl, (C₂-C₈)alkenyl, (C₂-C₈)alkynyl, (C₃-C₇)carbocycle, heterocycle, heteroaryl, aryl, haloaryl, haloheteroaryl, haloheterocycle, (C₁-C₈)haloalkyl and (C₁-C₈)heteroalkyl, or R_{q6} and R_{r6} together with the nitrogen to which they are attached form a 5, 6 or 7-membered heterocycle;

each Z^4 is independently selected from (C₁-C₈)alkyl, (C₂-C₈)alkenyl, (C₂-C₈)alkynyl, (C₃-C₇)carbocycle, aryl, heteroaryl, heterocycle, halogen, -CN, -OR_{n8}, -OC(O)R_{p8}, -OC(O)NR_{q8}R_{r8}, -SR_{n8}, -S(O)R_{p8}, -S(O)₂OH, -S(O)₂R_{p8}, -S(O)₂NR_{q8}R_{r8}, -NR_{q8}R_{r8}, -NR_{n8}COR_{p8}, -NR_{n8}CO₂R_{p8}, -NR_{n8}CONR_{q8}R_{r8}, -NR_{n8}S(O)₂R_{p8}, -NR_{n8}S(O)₂OR_{p8}, -NR_{n8}S(O)₂NR_{q8}R_{r8}, NO₂, -C(O)R_{n8}, -C(O)OR_{n8}, and -C(O)NR_{q8}R_{r8}, wherein any (C₃-C₇)carbocycle, aryl, heteroaryl and heterocycle of Z^4 is optionally substituted with one or more (e.g. 1, 2, 3, 4 or 5) Z^{4c} or Z^{4d} groups and wherein any (C₁-C₈)alkyl, (C₂-C₈)alkenyl and (C₂-C₈)alkynyl of Z^4 is optionally substituted with one or more (e.g. 1, 2, 3, 4 or 5) Z^{4c} groups;

each Z^{4c} is independently selected from (C₃-C₇)carbocycle, aryl, heteroaryl, heterocycle, halogen, -CN, -OR_{n9}, -OC(O)R_{p9}, -OC(O)NR_{q9}R_{r9}, -SR_{n9}, -S(O)R_{p9}, -S(O)₂OH, -S(O)₂R_{p9}, -S(O)₂NR_{q9}R_{r9}, -NR_{q9}R_{r9}, -NR_{n9}COR_{p9}, -NR_{n9}CO₂R_{p9}, -NR_{n9}CONR_{q9}R_{r9}, -NR_{n9}S(O)₂R_{p9}, -NR_{n9}S(O)₂OR_{p9}, -NR_{n9}S(O)₂NR_{q9}R_{r9}, NO₂, -C(O)R_{n9}, -C(O)OR_{n9}, -C(O)NR_{q9}R_{r9}, haloaryl, haloheteroaryl, haloheterocycle and (C₁-C₈)heteroalkyl;

each Z^{4d} is independently selected from (C₁-C₈)alkyl, (C₂-C₈)alkenyl, (C₂-C₈)alkynyl and (C₁-C₈)haloalkyl;

each R_{n8} is independently selected from H, (C₁-C₈)alkyl, (C₂-C₈)alkenyl, (C₂-C₈)alkynyl, (C₃-C₇)carbocycle, heterocycle, heteroaryl and aryl, wherein any (C₃-C₇)carbocycle, aryl, heteroaryl and heterocycle of R_{n8} is optionally substituted with one or more (e.g. 1, 2, 3, 4 or 5) Z^{4c} or Z^{4d} groups, and wherein any (C₁-C₈)alkyl, (C₂-C₈)alkenyl or (C₂-C₈)alkynyl of R_{n8} is optionally substituted with one or more (e.g. 1, 2, 3, 4 or 5) Z^{4c} groups;

each R_{p8} is independently selected from (C₁-C₈)alkyl, (C₁-C₆)haloalkyl, (C₂-C₈)alkenyl, (C₂-C₈)alkynyl, (C₃-C₇)carbocycle, heterocycle, heteroaryl and aryl, wherein any (C₃-C₇)carbocycle, aryl, heteroaryl and heterocycle of R_{p8} is optionally substituted with one or

more (e.g. 1, 2, 3, 4 or 5) Z^{4c} or Z^{4d} groups, and wherein any (C₁-C₈)alkyl, (C₂-C₈)alkenyl and (C₂-C₈)alkynyl of R_{p8} is optionally substituted with one or more (e.g. 1, 2, 3, 4 or 5) Z^{4c} groups;

R_{q8} and R_{r8} are each independently selected from H, (C₁-C₈)alkyl, (C₂-C₈)alkenyl, (C₂-C₈)alkynyl, (C₃-C₇)carbocycle, heterocycle, heteroaryl and aryl, wherein any (C₃-C₇)carbocycle, aryl, heteroaryl and heterocycle of R_{q8} or R_{r8} is optionally substituted with one or more (e.g. 1, 2, 3, 4 or 5) Z^{4c} or Z^{4d} groups, and wherein any (C₁-C₈)alkyl, (C₂-C₈)alkenyl and (C₂-C₈)alkynyl of R_{q8} or R_{r8} is optionally substituted with one or more (e.g. 1, 2, 3, 4 or 5) Z^{4c} groups, or R_{q8} and R_{r8} 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;

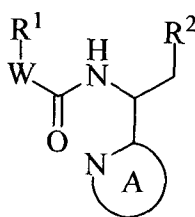
each R_{n9} is independently selected from H, (C₁-C₈)alkyl, (C₂-C₈)alkenyl, (C₂-C₈)alkynyl, (C₃-C₇)carbocycle, heterocycle, heteroaryl, aryl, haloaryl, haloheteroaryl, haloheterocycle, (C₁-C₈)haloalkyl and (C₁-C₈)heteroalkyl;

each R_{p9} is independently selected from (C₁-C₈)alkyl, (C₂-C₈)alkenyl, (C₂-C₈)alkynyl, (C₃-C₇)carbocycle, heterocycle, heteroaryl, aryl, haloaryl, haloheteroaryl, haloheterocycle, (C₁-C₈)haloalkyl and (C₁-C₈)heteroalkyl; and

R_{q9} and R_{r9} are each independently selected from H, (C₁-C₈)alkyl, (C₂-C₈)alkenyl, (C₂-C₈)alkynyl, (C₃-C₇)carbocycle, heterocycle, heteroaryl, aryl, haloaryl, haloheteroaryl, haloheterocycle, (C₁-C₈)haloalkyl and (C₁-C₈)heteroalkyl; or R_{q9} and R_{r9} together with the nitrogen to which they are attached form a 5, 6 or 7-membered heterocycle;

or a salt thereof.

In one embodiment, the invention provides a compound of the invention which is a compound of formula I':



I'

wherein:

A is a 6-membered heteroaryl comprising one or two nitrogens, wherein the 6-membered heteroaryl is substituted with one Z^1 group and optionally substituted with one or more (e.g. 1, 2, or 3) Z^2 groups;

W is CR^{3a}R^{3b}, O or NR⁴;

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^3 groups;

R^2 is a 6-membered aryl, 5-membered heteroaryl or 6-membered heteroaryl, wherein any 6-membered aryl, 5-membered heteroaryl or 6-membered heteroaryl of R^2 is optionally substituted with one or more (e.g. 1, 2 or 3) Z^4 groups;

each R^{3a} and R^{3b} is independently selected from H, halogen, (C_1-C_3) alkyl, (C_1-C_3) haloalkyl, (C_1-C_6) heteroalkyl, $-(C_1-C_6)$ alkylheteroaryl, $-(C_1-C_6)$ alkylheterocyclyl, $-NR_aR_b$, and $-NR_cCOR_d$; or R^{3a} and R^{3b} together with the carbon to which they are attached form a (C_3-C_6) carbocycle;

R^4 is selected from H, (C_1-C_6) alkyl, (C_3-C_6) carbocycle, $-(C_1-C_6)$ alkylaryl and $-(C_1-C_6)$ alkylheteroaryl;

R_a and R_b 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, aryl, haloaryl, haloheteroaryl, haloheterocycle, (C_1-C_8) haloalkyl and (C_1-C_8) heteroalkyl, or R_a and R_b together with the nitrogen to which they are attached form a 5, 6 or 7-membered heterocycle;

each R_c 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-C_8) haloalkyl and (C_1-C_8) heteroalkyl;

each R_d 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, aryl, haloaryl, haloheteroaryl, haloheterocycle, (C_1-C_8) haloalkyl and (C_1-C_8) heteroalkyl;

each Z^1 is independently selected from (C_1-C_8) alkyl, (C_2-C_8) alkenyl, (C_2-C_8) alkynyl, (C_3-C_7) carbocycle, aryl, heteroaryl, heterocycle and $-OR_{n1}$, wherein any (C_3-C_7) carbocycle, 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} groups and wherein any (C_1-C_8) alkyl, (C_2-C_8) alkenyl and (C_2-C_8) alkynyl of Z^1 is optionally substituted with one or more (e.g. 1, 2, 3, 4 or 5) Z^{1a} groups;

each Z^{1a} is independently selected from (C_3-C_7) carbocycle, aryl, heteroaryl, heterocycle, halogen, $-CN$, $-OR_{n2}$, $-OC(O)R_{p2}$, $-OC(O)NR_{q2}R_{r2}$, $-SR_{n2}$, $-S(O)R_{p2}$, $-S(O)_2OH$, $-S(O)_2R_{p2}$, $-S(O)_2NR_{q2}R_{r2}$, $-NR_{q2}R_{r2}$, $-NR_{n2}COR_{p2}$, $-NR_{n2}CO_2R_{p2}$, $-NR_{n2}CONR_{q2}R_{r2}$, $-NR_{n2}S(O)_2R_{p2}$, $-NR_{n2}S(O)_2OR_{p2}$, $-NR_{n2}S(O)_2NR_{q2}R_{r2}$, NO_2 , $-C(O)R_{n2}$, $-C(O)OR_{n2}$, and, $-C(O)NR_{p2}R_{q2}$, 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;

each Z^{1b} is independently selected from (C₁-C₈)alkyl, (C₂-C₈)alkenyl and (C₂-C₈)alkynyl, wherein any (C₁-C₈)alkyl, (C₂-C₈)alkenyl and (C₂-C₈)alkynyl of Z^{1b} is optionally substituted with one or more (e.g. 1, 2, 3, 4 or 5) Z^{1c} groups;

each Z^{1c} is independently selected from (C₃-C₇)carbocycle, aryl, heteroaryl, heterocycle, halogen, -CN, -OR_{n3}, -OC(O)R_{p3}, -OC(O)NR_{q3}R_{r3}, -SR_{n3}, -S(O)R_{p3}, -S(O)₂OH, -S(O)₂R_{p3}, -S(O)₂NR_{q3}R_{r3}, -NR_{q3}R_{r3}, -NR_{n3}COR_{p3}, -NR_{n3}CO₂R_{p3}, -NR_{n3}CONR_{q3}R_{r3}, -NR_{n3}S(O)₂R_{p3}, -NR_{n3}S(O)₂OR_{p3}, -NR_{n3}S(O)₂NR_{q3}R_{r3}, NO₂, -C(O)R_{n3}, -C(O)OR_{n3}, -C(O)NR_{q3}R_{r3}, haloaryl, haloheteroaryl, haloheterocycle and (C₁-C₈)heteroalkyl;

each Z^{1d} is independently selected from (C₁-C₈)alkyl, (C₂-C₈)alkenyl, (C₂-C₈)alkynyl and (C₁-C₈)haloalkyl;

each R_{n1} is independently selected from (C₁-C₈)alkyl, (C₂-C₈)alkenyl, (C₂-C₈)alkynyl, (C₃-C₇)carbocycle, heterocycle, heteroaryl and aryl, wherein any (C₃-C₇)carbocycle, aryl, heteroaryl and heterocycle of R_{n1} is optionally substituted with one or more (e.g. 1, 2, 3, 4 or 5) Z^{1a} or Z^{1b} groups, and wherein any (C₁-C₈)alkyl, (C₂-C₈)alkenyl and (C₂-C₈)alkynyl of R_{n1} is optionally substituted with one or more (e.g. 1, 2, 3, 4 or 5) Z^{1a} groups;

each R_{n2} is independently selected from H, (C₁-C₈)alkyl, (C₂-C₈)alkenyl, (C₂-C₈)alkynyl, (C₃-C₇)carbocycle, heterocycle, heteroaryl and aryl, wherein any (C₃-C₇)carbocycle, aryl, heteroaryl and heterocycle of R_{n2} is optionally substituted with one or more (e.g. 1, 2, 3, 4 or 5) Z^{1c} or Z^{1d} groups, and wherein any (C₁-C₈)alkyl, (C₂-C₈)alkenyl and (C₂-C₈)alkynyl of R_{n2} is optionally substituted with one or more (e.g. 1, 2, 3, 4 or 5) Z^{1c} groups;

each R_{p2} is independently selected from (C₁-C₈)alkyl, (C₂-C₈)alkenyl, (C₂-C₈)alkynyl, (C₃-C₇)carbocycle, heterocycle, heteroaryl and aryl, wherein any (C₃-C₇)carbocycle, aryl, heteroaryl and heterocycle of R_{p2} is optionally substituted with one or more (e.g. 1, 2, 3, 4 or 5) Z^{1c} or Z^{1d} groups, and wherein any (C₁-C₈)alkyl, (C₂-C₈)alkenyl and (C₂-C₈)alkynyl of R_{p2} is optionally substituted with one or more (e.g. 1, 2, 3, 4 or 5) Z^{1c} groups;

R_{q2} and R_{r2} are each independently selected from H, (C₁-C₈)alkyl, (C₂-C₈)alkenyl, (C₂-C₈)alkynyl, (C₃-C₇)carbocycle, heterocycle, heteroaryl and aryl, wherein any (C₃-C₇)carbocycle, aryl, heteroaryl and heterocycle of R_{q2} or R_{r2} is optionally substituted with one or more (e.g. 1, 2, 3, 4 or 5) Z^{1c} or Z^{1d} groups, and wherein any (C₁-C₈)alkyl, (C₂-C₈)alkenyl and (C₂-C₈)alkynyl of R_{q2} or R_{r2} is optionally substituted with one or more (e.g. 1, 2, 3, 4 or 5) Z^{1c} groups, or R_{q2} and R_{r2} 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;

each R_{n3} is independently selected from H, (C₁-C₈)alkyl, (C₂-C₈)alkenyl, (C₂-C₈)alkynyl, (C₃-C₇)carbocycle, heterocycle, heteroaryl, aryl, haloaryl, haloheteroaryl, haloheterocycle, (C₁-C₈)haloalkyl and (C₁-C₈)heteroalkyl;

each R_{p3} is independently selected from (C₁-C₈)alkyl, (C₂-C₈)alkenyl, (C₂-C₈)alkynyl, (C₃-C₇)carbocycle, heterocycle, heteroaryl, aryl, haloaryl, haloheteroaryl, haloheterocycle, (C₁-C₈)haloalkyl and (C₁-C₈)heteroalkyl;

R_{q3} and R_{r3} are each independently selected from H, (C₁-C₈)alkyl, (C₂-C₈)alkenyl, (C₂-C₈)alkynyl, (C₃-C₇)carbocycle, heterocycle, heteroaryl, aryl, haloaryl, haloheteroaryl, haloheterocycle, (C₁-C₈)haloalkyl and (C₁-C₈)heteroalkyl, or R_{q3} and R_{r3} together with the nitrogen to which they are attached form a 5, 6 or 7-membered heterocycle;

each Z^2 is independently selected from (C₁-C₆)alkyl, (C₁-C₆)haloalkyl, (C₃-C₇)carbocycle, halogen, CN, OH and -O(C₁-C₆)alkyl;

each Z^3 is independently selected from (C₁-C₈)alkyl, (C₂-C₈)alkenyl, (C₂-C₈)alkynyl, (C₃-C₇)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)₂OH, -S(O)₂R_{p4}, -S(O)₂NR_{q4}R_{r4}, -NR_{q4}R_{r4}, -NR_{n4}COR_{p4}, -NR_{n4}CO₂R_{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}, NO₂, -C(O)R_{n4}, -C(O)OR_{n4}, and -C(O)NR_{q4}R_{r4}, wherein any (C₃-C₇)carbocycle, aryl, heteroaryl and heterocycle of Z^3 is optionally substituted with one or more (e.g. 1, 2, 3, 4 or 5) Z^{3a} or Z^{3b} groups, and wherein any (C₁-C₈)alkyl, (C₂-C₈)alkenyl and (C₂-C₈)alkynyl of Z^3 is optionally substituted with one or more (e.g. 1, 2, 3, 4 or 5) Z^{3a} groups;

each Z^{3a} is independently selected from (C₃-C₇)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)₂OH, -S(O)₂R_{p5}, -S(O)₂NR_{q5}R_{r5}, -NR_{q5}R_{r5}, -NR_{n5}COR_{p5}, -NR_{n5}CO₂R_{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}, NO₂, -C(O)R_{n5}, -C(O)OR_{n5}, and -C(O)NR_{q5}R_{r5}, wherein any (C₃-C₇)carbocycle, aryl, heteroaryl and heterocycle of Z^{3a} is optionally substituted with one or more (e.g. 1, 2, 3, 4 or 5) Z^{3c} or Z^{3d} groups;

each Z^{3b} is independently selected from (C₁-C₈)alkyl, (C₂-C₈)alkenyl and (C₂-C₈)alkynyl, wherein any (C₁-C₈)alkyl, (C₂-C₈)alkenyl and (C₂-C₈)alkynyl of Z^{3b} is optionally substituted with one or more (e.g. 1, 2, 3, 4 or 5) Z^{3c} groups;

each Z^{3c} is independently selected from (C₃-C₇)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)₂OH, -S(O)₂R_{p6}, -S(O)₂NR_{q6}R_{r6}, -NR_{q6}R_{r6}, -NR_{n6}COR_{p6}, -NR_{n6}CO₂R_{p6}, -NR_{n6}CONR_{q6}R_{r6}, -NR_{n6}S(O)₂R_{p6},

$-\text{NR}_{n6}\text{S}(\text{O})_2\text{OR}_{p6}$, $-\text{NR}_{n6}\text{S}(\text{O})_2\text{NR}_{q6}\text{R}_{r6}$, NO_2 , $-\text{C}(\text{O})\text{R}_{n6}$, $-\text{C}(\text{O})\text{OR}_{n6}$, $-\text{C}(\text{O})\text{NR}_{q6}\text{R}_{r6}$, haloaryl, haloheteroaryl, haloheterocycle and $(\text{C}_1\text{-C}_8)\text{heteroalkyl}$;

each Z^{3d} is independently selected from of $(\text{C}_1\text{-C}_8)\text{alkyl}$, $(\text{C}_2\text{-C}_8)\text{alkenyl}$, $(\text{C}_2\text{-C}_8)\text{alkynyl}$, and $(\text{C}_1\text{-C}_8)\text{haloalkyl}$;

5 each R_{n4} is independently selected from H, $(\text{C}_1\text{-C}_8)\text{alkyl}$, $(\text{C}_2\text{-C}_8)\text{alkenyl}$, $(\text{C}_2\text{-C}_8)\text{alkynyl}$, $(\text{C}_3\text{-C}_7)\text{carbocycle}$, heterocycle, heteroaryl and aryl, wherein any $(\text{C}_3\text{-C}_7)\text{carbocycle}$, aryl, heteroaryl and heterocycle of R_{n4} is optionally substituted with one or more (e.g. 1, 2, 3, 4 or 5) Z^{3a} or Z^{3b} groups, and wherein any $(\text{C}_1\text{-C}_8)\text{alkyl}$, $(\text{C}_2\text{-C}_8)\text{alkenyl}$ and $(\text{C}_2\text{-C}_8)\text{alkynyl}$ of R_{n4} is optionally substituted with one or more (e.g. 1, 2, 3, 4 or 5) Z^{3a} groups;

10 each R_{p4} is independently selected from $(\text{C}_1\text{-C}_8)\text{alkyl}$, $(\text{C}_2\text{-C}_8)\text{alkenyl}$, $(\text{C}_2\text{-C}_8)\text{alkynyl}$, $(\text{C}_3\text{-C}_7)\text{carbocycle}$, heterocycle, heteroaryl and aryl, wherein any $(\text{C}_3\text{-C}_7)\text{carbocycle}$, aryl, heteroaryl, or heterocycle of R_{p4} is optionally substituted with one or more (e.g. 1, 2, 3, 4 or 5) Z^{3a} or Z^{3b} groups, and wherein any $(\text{C}_1\text{-C}_8)\text{alkyl}$, $(\text{C}_2\text{-C}_8)\text{alkenyl}$ or $(\text{C}_2\text{-C}_8)\text{alkynyl}$ of R_{p4} is optionally substituted with one or more (e.g. 1, 2, 3, 4 or 5) Z^{3a} groups;

15 R_{q4} and R_{r4} are each independently selected from H, $(\text{C}_1\text{-C}_8)\text{alkyl}$, $(\text{C}_2\text{-C}_8)\text{alkenyl}$, $(\text{C}_2\text{-C}_8)\text{alkynyl}$, $(\text{C}_3\text{-C}_7)\text{carbocycle}$, heterocycle, heteroaryl and aryl, wherein any $(\text{C}_3\text{-C}_7)\text{carbocycle}$, aryl, heteroaryl and heterocycle of R_{q4} or R_{r4} is optionally substituted with one or more (e.g. 1, 2, 3, 4 or 5) Z^{3a} or Z^{3b} groups, and wherein any $(\text{C}_1\text{-C}_8)\text{alkyl}$, $(\text{C}_2\text{-C}_8)\text{alkenyl}$ and $(\text{C}_2\text{-C}_8)\text{alkynyl}$ of R_{q4} or R_{r4} is optionally substituted with one or more (e.g. 1, 2, 3, 4 or 5) Z^{3a} groups, or R_{q4} and R_{r4} 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^{3a} or Z^{3b} groups;

20 each R_{n5} is independently selected from H, $(\text{C}_1\text{-C}_8)\text{alkyl}$, $(\text{C}_2\text{-C}_8)\text{alkenyl}$, $(\text{C}_2\text{-C}_8)\text{alkynyl}$, $(\text{C}_3\text{-C}_7)\text{carbocycle}$, heterocycle, heteroaryl and aryl, wherein any $(\text{C}_3\text{-C}_7)\text{carbocycle}$, aryl, heteroaryl and heterocycle of R_{n5} is optionally substituted with one or more (e.g. 1, 2, 3, 4 or 5) Z^{3c} or Z^{3d} groups, and wherein any $(\text{C}_1\text{-C}_8)\text{alkyl}$, $(\text{C}_2\text{-C}_8)\text{alkenyl}$ and $(\text{C}_2\text{-C}_8)\text{alkynyl}$ of R_{n5} is optionally substituted with one or more (e.g. 1, 2, 3, 4 or 5) Z^{3c} groups;

25 each R_{p5} is independently selected from $(\text{C}_1\text{-C}_8)\text{alkyl}$, $(\text{C}_2\text{-C}_8)\text{alkenyl}$, $(\text{C}_2\text{-C}_8)\text{alkynyl}$, $(\text{C}_3\text{-C}_7)\text{carbocycle}$, heterocycle, heteroaryl and aryl, wherein any $(\text{C}_3\text{-C}_7)\text{carbocycle}$, aryl, heteroaryl and heterocycle of R_{p5} is optionally substituted with one or more (e.g. 1, 2, 3, 4 or 5) Z^{3c} or Z^{3d} groups, and wherein any $(\text{C}_1\text{-C}_8)\text{alkyl}$, $(\text{C}_2\text{-C}_8)\text{alkenyl}$ and $(\text{C}_2\text{-C}_8)\text{alkynyl}$ of R_{p5} is optionally substituted with one or more (e.g. 1, 2, 3, 4 or 5) Z^{3c} groups;

R_{q5} and R_{r5} are each independently selected from H, (C₁-C₈)alkyl, (C₂-C₈)alkenyl, (C₂-C₈)alkynyl, (C₃-C₇)carbocycle, heterocycle, heteroaryl and aryl, wherein any (C₃-C₇)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^{3c} or Z^{3d} groups, and wherein any (C₁-C₈)alkyl, (C₂-C₈)alkenyl and (C₂-C₈)alkynyl of R_{q5} or R_{r5} is optionally substituted with one or more (e.g. 1, 2, 3, 4 or 5) Z^{3c} 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^{3c} or Z^{3d} groups;

each R_{n6} is independently selected from H, (C₁-C₈)alkyl, (C₂-C₈)alkenyl, (C₂-C₈)alkynyl, (C₃-C₇)carbocycle, heterocycle, heteroaryl, aryl, haloaryl, haloheteroaryl, haloheterocycle, (C₁-C₈)haloalkyl and (C₁-C₈)heteroalkyl;

each R_{p6} is independently selected from (C₁-C₈)alkyl, (C₂-C₈)alkenyl, (C₂-C₈)alkynyl, (C₃-C₇)carbocycle, heterocycle, heteroaryl, aryl, haloaryl, haloheteroaryl, haloheterocycle, (C₁-C₈)haloalkyl and (C₁-C₈)heteroalkyl;

R_{q6} and R_{r6} are each independently selected from H, (C₁-C₈)alkyl, (C₂-C₈)alkenyl, (C₂-C₈)alkynyl, (C₃-C₇)carbocycle, heterocycle, heteroaryl, aryl, haloaryl, haloheteroaryl, haloheterocycle, (C₁-C₈)haloalkyl and (C₁-C₈)heteroalkyl, or R_{q6} and R_{r6} together with the nitrogen to which they are attached form a 5, 6 or 7-membered heterocycle;

each Z^4 is independently selected from (C₁-C₈)alkyl, (C₂-C₈)alkenyl, (C₂-C₈)alkynyl, (C₃-C₇)carbocycle, aryl, heteroaryl, heterocycle, halogen, -CN, -OR_{n8}, -OC(O)R_{p8}, -OC(O)NR_{q8}R_{r8}, -SR_{n8}, -S(O)R_{p8}, -S(O)₂OH, -S(O)₂R_{p8}, -S(O)₂NR_{q8}R_{r8}, -NR_{q8}R_{r8}, -NR_{n8}COR_{p8}, -NR_{n8}CO₂R_{p8}, -NR_{n8}CONR_{q8}R_{r8}, -NR_{n8}S(O)₂R_{p8}, -NR_{n8}S(O)₂OR_{p8}, -NR_{n8}S(O)₂NR_{q8}R_{r8}, NO₂, -C(O)R_{n8}, -C(O)OR_{n8}, and -C(O)NR_{q8}R_{r8}, wherein any (C₃-C₇)carbocycle, aryl, heteroaryl and heterocycle of Z^4 is optionally substituted with one or more (e.g. 1, 2, 3, 4 or 5) Z^{4c} or Z^{4d} groups and wherein any (C₁-C₈)alkyl, (C₂-C₈)alkenyl and (C₂-C₈)alkynyl of Z^4 is optionally substituted with one or more (e.g. 1, 2, 3, 4 or 5) Z^{4c} groups;

each Z^{4c} is independently selected from (C₃-C₇)carbocycle, aryl, heteroaryl, heterocycle, halogen, -CN, -OR_{n9}, -OC(O)R_{p9}, -OC(O)NR_{q9}R_{r9}, -SR_{n9}, -S(O)R_{p9}, -S(O)₂OH, -S(O)₂R_{p9}, -S(O)₂NR_{q9}R_{r9}, -NR_{q9}R_{r9}, -NR_{n9}COR_{p9}, -NR_{n9}CO₂R_{p9}, -NR_{n9}CONR_{q9}R_{r9}, -NR_{n9}S(O)₂R_{p9}, -NR_{n9}S(O)₂OR_{p9}, -NR_{n9}S(O)₂NR_{q9}R_{r9}, NO₂, -C(O)R_{n9}, -C(O)OR_{n9}, -C(O)NR_{q9}R_{r9}, haloaryl, haloheteroaryl, haloheterocycle and (C₁-C₈)heteroalkyl;

each Z^{4d} is independently selected from (C₁-C₈)alkyl, (C₂-C₈)alkenyl, (C₂-C₈)alkynyl and (C₁-C₈)haloalkyl;

each R_{n8} is independently selected from H, (C₁-C₈)alkyl, (C₂-C₈)alkenyl, (C₂-C₈)alkynyl, (C₃-C₇)carbocycle, heterocycle, heteroaryl and aryl, wherein any (C₃-C₇)carbocycle, aryl, heteroaryl and heterocycle of R_{n8} is optionally substituted with one or more (e.g. 1, 2, 3, 4 or 5) Z^{4c} or Z^{4d} groups, and wherein any (C₁-C₈)alkyl, (C₂-C₈)alkenyl or (C₂-C₈)alkynyl of R_{n8} is optionally substituted with one or more (e.g. 1, 2, 3, 4 or 5) Z^{4c} groups;

each R_{p8} is independently selected from (C₁-C₈)alkyl, (C₁-C₆)haloalkyl, (C₂-C₈)alkenyl, (C₂-C₈)alkynyl, (C₃-C₇)carbocycle, heterocycle, heteroaryl and aryl, wherein any (C₃-C₇)carbocycle, aryl, heteroaryl and heterocycle of R_{p8} is optionally substituted with one or more (e.g. 1, 2, 3, 4 or 5) Z^{4c} or Z^{4d} groups, and wherein any (C₁-C₈)alkyl, (C₂-C₈)alkenyl and (C₂-C₈)alkynyl of R_{p8} is optionally substituted with one or more (e.g. 1, 2, 3, 4 or 5) Z^{4c} groups;

R_{q8} and R_{r8} are each independently selected from H, (C₁-C₈)alkyl, (C₂-C₈)alkenyl, (C₂-C₈)alkynyl, (C₃-C₇)carbocycle, heterocycle, heteroaryl and aryl, wherein any (C₃-C₇)carbocycle, aryl, heteroaryl and heterocycle of R_{q8} or R_{r8} is optionally substituted with one or more (e.g. 1, 2, 3, 4 or 5) Z^{4c} or Z^{4d} groups, and wherein any (C₁-C₈)alkyl, (C₂-C₈)alkenyl and (C₂-C₈)alkynyl of R_{q8} or R_{r8} is optionally substituted with one or more (e.g. 1, 2, 3, 4 or 5) Z^{4c} groups, or R_{q8} and R_{r8} 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;

each R_{n9} is independently selected from H, (C₁-C₈)alkyl, (C₂-C₈)alkenyl, (C₂-C₈)alkynyl, (C₃-C₇)carbocycle, heterocycle, heteroaryl, aryl, haloaryl, haloheteroaryl, haloheterocycle, (C₁-C₈)haloalkyl and (C₁-C₈)heteroalkyl;

each R_{p9} is independently selected from (C₁-C₈)alkyl, (C₂-C₈)alkenyl, (C₂-C₈)alkynyl, (C₃-C₇)carbocycle, heterocycle, heteroaryl, aryl, haloaryl, haloheteroaryl, haloheterocycle, (C₁-C₈)haloalkyl and (C₁-C₈)heteroalkyl; and

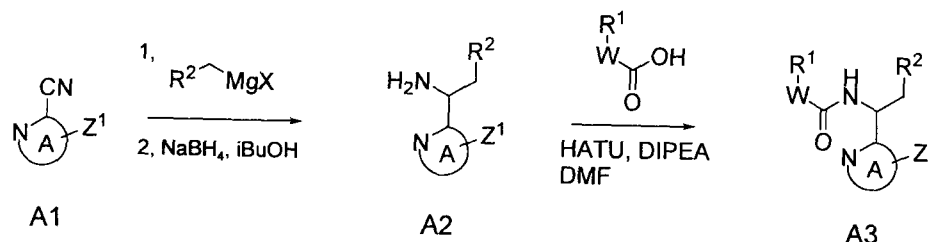
R_{q9} and R_{r9} are each independently selected from H, (C₁-C₈)alkyl, (C₂-C₈)alkenyl, (C₂-C₈)alkynyl, (C₃-C₇)carbocycle, heterocycle, heteroaryl, aryl, haloaryl, haloheteroaryl, haloheterocycle, (C₁-C₈)haloalkyl and (C₁-C₈)heteroalkyl; or R_{q9} and R_{r9} together with the nitrogen to which they are attached form a 5, 6 or 7-membered heterocycle;

or a salt thereof.

General Synthetic Procedures

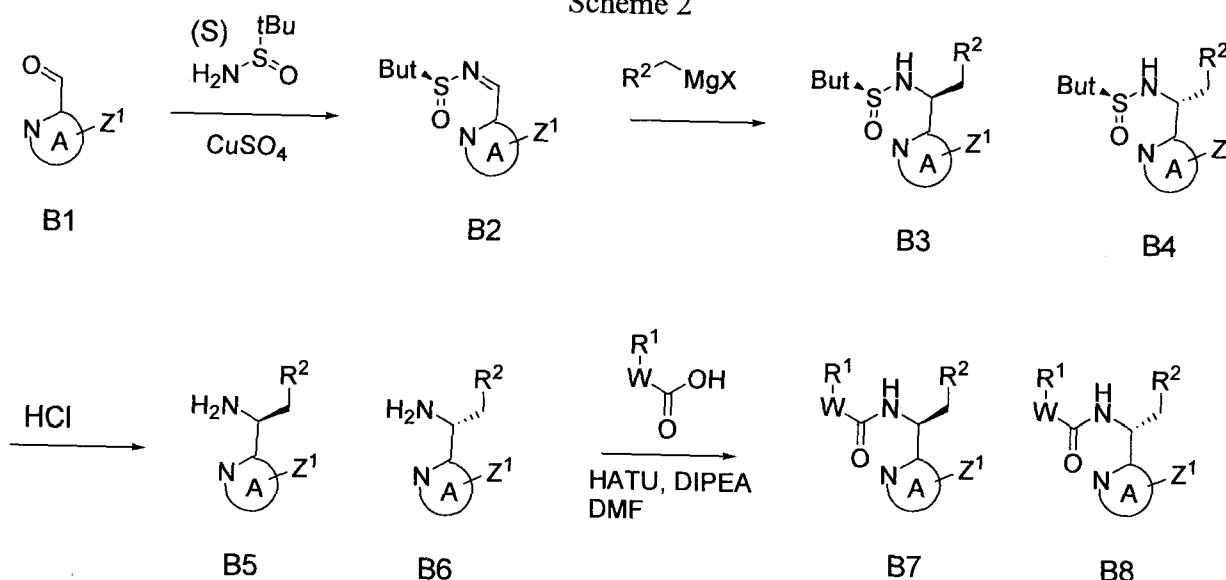
Schemes 1, 2 and 3 describe methods that can be used to prepare compounds of formula I.

Scheme 1



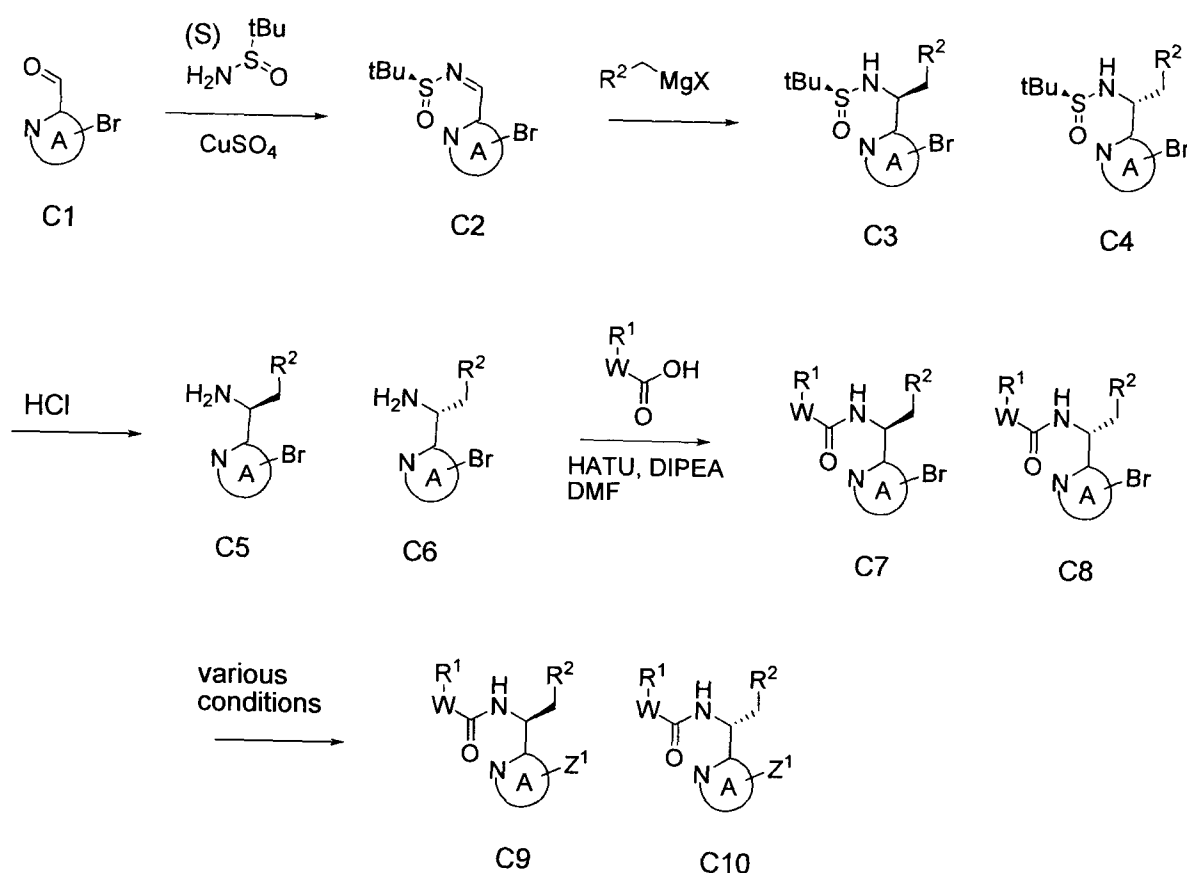
Scheme 1 describes a general synthetic route which can be used to prepare compounds of formula I. An appropriately substituted heteroaryl nitrile may be reacted with a Grignard reagent followed by reduction to provide compounds of formula A2. The amine can be coupled to a variety of carboxylic acid derivatives to provide compounds of formula A3.

Scheme 2



Scheme 2 describes a general stereoselective route which can be used to prepare compounds of formula I. Heteroaryl aldehydes of formula B1 can be condensed with a chiral auxiliary to provide a stereoselective addition of a nucleophilic reagent. Depicted in Scheme 2 is the condensation of an appropriately substituted heterocyclic aldehyde B1 with tert-butane sulfonamide and the addition of a Grignard reagent to provide a mixture of B3 and B4 enriched in B3. This mixture may be separated by column chromatography on silica gel to provide pure diastereomers. Removal of the auxiliary provides amines B5 and B6 which can be coupled to a variety of carboxylic acids to provide compounds of formula B7 and B8.

Scheme 3



Scheme 3 describes a general stereoselective route which can be used to prepare compounds of formula I. Heteroaryl aldehydes of formula B1 can be condensed with a chiral auxiliary to provide a stereoselective addition of a nucleophilic reagent. Depicted in Scheme 3 is the condensation of an bromo-substituted heterocyclic aldehyde C1 with (S) tert-butane sulfonamide and the addition of a Grignard reagent to provide a mixture of C3 and C4 enriched in C3. This mixture may be separated by column chromatography on silica gel to provide pure diastereomers. Removal of the auxiliary provides amines C5 and C6 which can be coupled to a variety of carboxylic acids to provide heteroaryl compounds of formula C7 and C8. Diversification of C7 and C8 may be accomplished by a variety of methods including metal catalyzed cross coupling reactions such as Suzuki couplings and Sonogashira couplings.

Prodrugs

In one embodiment, the invention provides for a prodrug of a compound of the invention. The term “prodrug” as used herein refers to any compound that when administered to a biological system generates a compound of the invention that inhibits the replication of HIV (“the active inhibitory compound”). The compound may be formed from the prodrug as a result

of: (i) spontaneous chemical reaction(s), (ii) enzyme catalyzed chemical reaction(s), (iii) photolysis, and/or (iv) metabolic chemical reaction(s).

“Prodrug moiety” refers to a labile functional group which separates from the active inhibitory compound during metabolism, systemically, inside a cell, by hydrolysis, enzymatic cleavage, or by some other process (Bundgaard, Hans, “Design and Application of Prodrugs” in A Textbook of Drug Design and Development (1991), P. Krogsgaard-Larsen and H. Bundgaard, Eds. Harwood Academic Publishers, pp. 113-191). Enzymes which are capable of an enzymatic activation mechanism with the prodrug compounds of the invention include, but are not limited to, amidases, esterases, microbial enzymes, phospholipases, cholinesterases, and phosphatases.

Prodrug moieties can serve to enhance solubility, absorption and lipophilicity to optimize drug delivery, bioavailability and efficacy. A prodrug moiety may include an active metabolite or drug itself.

Exemplary prodrug moieties include the hydrolytically sensitive or labile acyloxymethyl esters $-\text{CH}_2\text{OC}(=\text{O})\text{R}^{99}$ and acyloxymethyl carbonates $-\text{CH}_2\text{OC}(=\text{O})\text{OR}^{99}$ where R^{99} is C_1 – C_6 alkyl, C_1 – C_6 substituted alkyl, C_6 – C_{20} aryl or C_6 – C_{20} substituted aryl. The acyloxyalkyl ester was first used as a prodrug strategy for carboxylic acids and then applied to phosphates and phosphonates by Farquhar et al. (1983) *J. Pharm. Sci.* 72: 324; also US Patent Nos. 4816570, 4968788, 5663159 and 5792756. Subsequently, the acyloxyalkyl ester was used to deliver phosphonic acids across cell membranes and to enhance oral bioavailability. A close variant of the acyloxyalkyl ester, the alkoxycarbonyloxyalkyl ester (carbonate), may also enhance oral bioavailability as a prodrug moiety in the compounds of the combinations of the invention. An exemplary acyloxymethyl ester is pivaloyloxymethoxy, (POM) $-\text{CH}_2\text{OC}(=\text{O})\text{C}(\text{CH}_3)_3$. An exemplary acyloxymethyl carbonate prodrug moiety is pivaloyloxymethylcarbonate (POC) $-\text{CH}_2\text{OC}(=\text{O})\text{OC}(\text{CH}_3)_3$.

Aryl esters of phosphorus groups, especially phenyl esters, are reported to enhance oral bioavailability (De Lombaert et al. (1994) *J. Med. Chem.* 37: 498). Phenyl esters containing a carboxylic ester ortho to a phosphate have also been described (Khamnei and Torrence, (1996) *J. Med. Chem.* 39:4109-4115). Benzyl esters are reported to generate parent phosphonic acids. In some cases, substituents at the *ortho*- or *para*- position may accelerate the hydrolysis. Benzyl analogs with an acylated phenol or an alkylated phenol may generate the phenolic compound through the action of enzymes, *e.g.*, esterases, oxidases, etc., which in turn undergoes cleavage at the benzylic C–O bond to generate phosphoric acid and a quinone methide intermediate. Examples of this class of prodrugs are described by Mitchell et al. (1992) *J. Chem. Soc. Perkin*

Trans. II 2345; Glazier WO 91/19721. Still other benzylic prodrugs have been described containing a carboxylic ester-containing group attached to the benzylic methylene (Glazier WO 91/19721). Thio-containing prodrugs are reported to be useful for the intracellular delivery of phosphonate drugs. These proesters contain an ethylthio group in which the thiol group is either
5 esterified with an acyl group or combined with another thiol group to form a disulfide. Deesterification or reduction of the disulfide generates the free thio intermediate which subsequently breaks down to the phosphoric acid and episulfide (Puech et al. (1993) *Antiviral Res.*, 22: 155-174; Benzaria et al. (1996) *J. Med. Chem.* 39: 4958).

10 Combination Therapy

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

In one embodiment, the invention provides pharmaceutical compositions comprising a compound of the present invention, 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 of the
20 present invention can be any anti-HIV agent.

In one embodiment, the invention provides pharmaceutical compositions comprising a compound of the present invention, 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,
25 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.

In another embodiment, the invention provides pharmaceutical compositions comprising
30 a compound of the present invention, or a pharmaceutically acceptable salt thereof, in combination with at least one additional therapeutic agent selected from the group consisting of:

(1) HIV protease inhibiting compounds selected from the group consisting of amprenavir, atazanavir, fosamprenavir, indinavir, lopinavir, ritonavir, nelfinavir, saquinavir,

tipranavir, brexanavir, 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;

(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, MIV-150, and TMC-120, rilpivirene, BILR 355 BS, VRX 840773, UK-453061, and RDEA806;

(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, $\pm$ -FTC, D-d4FC, emtricitabine, phosphazide, fozivudine tidoxil, apricitabine (AVX754), amdoxovir, KP-1461, and fosavudine tidoxil (formerly HDP 99.0003), ;

(4) HIV nucleotide inhibitors of reverse transcriptase selected from the group consisting of tenofovir, tenofovir disoproxil fumarate, GS-7340 (Gilead Sciences), adefovir, adefovir dipivoxil, CMX-001 (Chimerix) or CMX-157 (Chimerix)

(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 and dolutegravir;

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

(7) the CXCR4 inhibitor AMD-070;

(8) the entry inhibitor SP01A;

(9) the gp120 inhibitor BMS-488043;

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

(11) CCR5 inhibitors selected from the group consisting of aplaviroc, vicriviroc, maraviroc, PRO-140, INCB15050, PF-232798 (Pfizer), and CCR5mAb004;

(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).

In another embodiment, the invention provides pharmaceutical compositions comprising a compound of the present invention, or a pharmaceutically acceptable salt thereof, in combination with two, three, four or more additional therapeutic agents. For example, a compound of the present invention, or a pharmaceutically acceptable salt, thereof, is combined
5 with two, three, four or more additional therapeutic agents selected from the classes 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. The two, three four or more
10 additional therapeutic agents can be different therapeutic agents selected from the same class of therapeutic agents, or they can be selected from different classes of therapeutic agents.

In one embodiment, the invention provides for a combination pharmaceutical agent comprising:

- a) a compound of the invention (e.g. a compound of Formula I), or a
15 pharmaceutically acceptable salt, thereof; and
- b) at least one additional active agent which is suitable for treating an HIV infection.

In another embodiment, the invention provides a combination pharmaceutical agent comprising:

- a) a compound of the invention (e.g. a compound of Formula I), or a
20 pharmaceutically acceptable salt thereof; and
- b) 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.
25

It is also possible to combine any compound of the invention 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
30 administrations.

It is also possible to co-administer a compound of the invention with one or more other active therapeutic agents. Co-administration of a compound of the invention with one or more other active therapeutic agents generally refers to simultaneous or sequential administration of a

compound of the invention and one or more other active therapeutic agents, such that therapeutically effective amounts of the compound of the invention and one or more other active therapeutic agents are both present in the body of the patient.

Co-administration includes administration of unit dosages of the compounds of the invention before or after administration of unit dosages of one or more other active therapeutic agents, for example, administration of the compounds of the invention within seconds, minutes, or hours of the administration of one or more other active therapeutic agents. For example, a unit dose of a compound of the invention can be administered first, followed within seconds or minutes by administration of a unit dose of one or more other active therapeutic agents.

Alternatively, a unit dose of one or more other therapeutic agents can be administered first, followed by administration of a unit dose of a compound of the invention within seconds or minutes. In some cases, it may be desirable to administer a unit dose of a compound of the invention first, followed, after a period of hours (e.g., 1-12 hours), by administration of a unit dose of one or more other active therapeutic agents. In other cases, it may be desirable to administer a unit dose of one or more other active therapeutic agents first, followed, after a period of hours (e.g., 1-12 hours), by administration of a unit dose of a compound of the invention.

The combination therapy may provide "synergy" and "synergistic effect", *i.e.* the effect achieved when the active ingredients used together is greater than the sum of the effects that results from using the compounds separately. A synergistic effect may be attained when the active ingredients are: (1) co-formulated and administered or delivered simultaneously in a combined formulation; (2) delivered by alternation or in parallel as separate formulations; or (3) by some other regimen. When delivered in alternation therapy, a synergistic effect may be attained when the compounds are administered or delivered sequentially, e.g., in separate tablets, pills or capsules, or by different injections in separate syringes. In general, during alternation therapy, an effective dosage of each active ingredient is administered sequentially, *i.e.* serially, whereas in combination therapy, effective dosages of two or more active ingredients are administered together.

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 of the present invention, 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 drug for treating HIV.

5 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 of the present invention, 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:

10 (1) HIV protease inhibiting compounds selected from the group consisting of amprenavir, atazanavir, fosamprenavir, indinavir, lopinavir, ritonavir, nelfinavir, saquinavir, tipranavir, brexanavir, 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;

15 (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, MIV-150, and TMC-120, rilpivirene, BILR 355 BS, VRX 840773, UK-453061, and RDEA806;

20 (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, $\pm$ -FTC, D-d4FC, emtricitabine, phosphazide, fozivudine tidoxil, apricitibine (AVX754), amdoxovir, KP-1461, and fosalvudine tidoxil (formerly HDP 99.0003), ;

25 (4) HIV nucleotide inhibitors of reverse transcriptase selected from the group consisting of tenofovir, tenofovir disoproxil fumarate, GS-7340 (Gilead Sciences), adefovir, adefovir dipivoxil, CMX-001 (Chimerix) or CMX-157 (Chimerix)

30 (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 and dolutegravir;

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

(7) the CXCR4 inhibitor AMD-070;

(8) the entry inhibitor SP01A;

5 (9) the gp120 inhibitor BMS-488043;

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

(11) CCR5 inhibitors selected from the group consisting of aplaviroc, vicriviroc, maraviroc, PRO-140, INCB15050, PF-232798 (Pfizer), and CCR5mAb004;

10 (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).

Pharmaceutical Formulations

15 The compounds of this invention are formulated with conventional carriers and excipients, which will be selected in accord with ordinary practice. Tablets will contain excipients, 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
20 antioxidants, chelating agents such as EDTA, carbohydrates such as dextrin, hydroxyalkylcellulose, hydroxyalkylmethylcellulose, stearic acid and the like. The pH of the formulations ranges from about 3 to about 11, but is ordinarily about 7 to 10.

While it is possible for the active ingredients to be administered alone it may be preferable to present them as pharmaceutical formulations. The formulations, both for
25 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.

30 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 the carrier 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.

Formulations of the present invention suitable for oral administration may be presented
5 as discrete units such as capsules, cachets or tablets each containing a predetermined amount of the active ingredient; as a powder or granules; as a solution or a suspension in an aqueous or non-aqueous liquid; or as an oil-in-water liquid emulsion or a water-in-oil liquid emulsion. The active ingredient may also be administered as a bolus, electuary or paste.

A tablet is made by compression or molding, optionally with one or more accessory
10 ingredients. Compressed tablets may be prepared by compressing in a suitable machine the active ingredient in a free-flowing form such as a powder or granules, optionally mixed with a binder, lubricant, inert diluent, preservative, surface active or dispersing agent. Molded tablets may be made by molding in a suitable machine a mixture of the powdered active ingredient moistened with an inert liquid diluent. The tablets may optionally be coated or scored and
15 optionally are formulated so as to provide slow or controlled release of the active ingredient therefrom.

For administration to the eye or other external tissues *e.g.*, mouth and skin, the formulations are preferably applied as a topical ointment or cream containing the active ingredient(s) in an amount of, for example, 0.075 to 20% w/w (including active ingredient(s) in
20 a range between 0.1% and 20% in increments of 0.1% w/w such as 0.6% w/w, 0.7% w/w, etc.), preferably 0.2 to 15% w/w and most preferably 0.5 to 10% w/w. When formulated in an ointment, the active ingredients may be employed with either a paraffinic or a water-miscible ointment base. Alternatively, the active ingredients may be formulated in a cream with an oil-in-water cream base.

25 If desired, the aqueous phase of the cream base may include, for example, at least 30% w/w of a polyhydric alcohol, *i.e.* an alcohol having two or more hydroxyl groups such as propylene glycol, butane 1,3-diol, mannitol, sorbitol, glycerol and polyethylene glycol (including PEG 400) and mixtures thereof. The topical formulations may desirably include a compound which enhances absorption or penetration of the active ingredient through the skin or
30 other affected areas. Examples of such dermal penetration enhancers include dimethyl sulphoxide and related analogs.

The oily phase of the emulsions of this invention may be constituted from known ingredients in a known manner. While the phase may comprise merely an emulsifier (otherwise

known as an emulgent), it desirably comprises a mixture of at least one emulsifier with a fat or an oil or with both a fat and an oil. Preferably, a hydrophilic emulsifier is included together with a lipophilic emulsifier which acts as a stabilizer. It is also preferred to include both an oil and a fat. Together, the emulsifier(s) with or without stabilizer(s) make up the so-called emulsifying wax, and the wax together with the oil and fat make up the so-called emulsifying ointment base which forms the oily dispersed phase of the cream formulations.

Emulgents and emulsion stabilizers suitable for use in the formulation of the invention include Tween[®] 60, Span[®] 80, cetostearyl alcohol, benzyl alcohol, myristyl alcohol, glyceryl mono-stearate and sodium lauryl sulfate.

The choice of suitable oils or fats for the formulation is based on achieving the desired cosmetic properties. The cream should preferably be a non-greasy, non-staining and washable product with suitable consistency to avoid leakage from tubes or other containers. Straight or branched chain, mono- or dibasic alkyl esters such as di-isoadipate, isocetyl stearate, propylene glycol diester of coconut fatty acids, isopropyl myristate, decyl oleate, isopropyl palmitate, butyl stearate, 2-ethylhexyl palmitate or a blend of branched chain esters known as Crodamol CAP may be used, the last three being preferred esters. These may be used alone or in combination depending on the properties required. Alternatively, high melting point lipids such as white soft paraffin and/or liquid paraffin or other mineral oils are used.

Pharmaceutical formulations according to the present invention comprise one or more compounds of the invention 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.

Formulations for oral use may be also presented as hard gelatin capsules where the active ingredient is mixed with an inert solid diluent, for example calcium phosphate or kaolin, or as soft gelatin capsules wherein the active ingredient is mixed with water or an oil medium, such as peanut oil, liquid paraffin or olive oil.

Aqueous suspensions of the invention contain the active materials in admixture with excipients suitable for the manufacture of aqueous suspensions. Such excipients include a suspending agent, such as sodium carboxymethylcellulose, methylcellulose, hydroxypropyl methylcellulose, sodium alginate, polyvinylpyrrolidone, gum tragacanth and gum acacia, and dispersing or wetting agents such as a naturally occurring phosphatide (*e.g.*, lecithin), a condensation product of an alkyl oxide with a fatty acid (*e.g.*, polyoxyethylene stearate), a condensation product of ethylene oxide with a long chain aliphatic alcohol (*e.g.*, heptadecaethyleneoxycetanol), a condensation product of ethylene oxide with a partial ester derived from a fatty acid and a hexitol anhydride (*e.g.*, polyoxyethylene sorbitan monooleate). The aqueous suspension may also contain one or more preservatives such as ethyl or n-propyl p-hydroxy-benzoate, one or more coloring agents, one or more flavoring agents and one or more sweetening agents, such as sucrose or saccharin.

Oil suspensions may be formulated by suspending the active ingredient in a vegetable oil, such as arachis oil, olive oil, sesame oil or coconut oil, or in a mineral oil such as liquid paraffin. The oral suspensions may contain a thickening agent, such as beeswax, hard paraffin or cetyl alcohol. Sweetening agents, such as those set forth above, and flavoring agents may be added to provide a palatable oral preparation. These compositions may be preserved by the addition of an antioxidant such as ascorbic acid.

Dispersible powders and granules of the invention suitable for preparation of an aqueous suspension by the addition of water provide the active ingredient in admixture with a dispersing or wetting agent, a suspending agent, and one or more preservatives. Suitable dispersing or wetting agents and suspending agents are exemplified by those disclosed above. Additional excipients, for example sweetening, flavoring and coloring agents, may also be present.

The pharmaceutical compositions of the invention may also be in the form of oil-in-water emulsions. The oily phase may be a vegetable oil, such as olive oil or arachis oil, a mineral oil, such as liquid paraffin, or a mixture of these. Suitable emulsifying agents include naturally-occurring gums, such as gum acacia and gum tragacanth, naturally occurring
5 phosphatides, such as soybean lecithin, esters or partial esters derived from fatty acids and hexitol anhydrides, such as sorbitan monooleate, and condensation products of these partial esters with ethylene oxide, such as polyoxyethylene sorbitan monooleate. The emulsion may also contain sweetening and flavoring agents. Syrups and elixirs may be formulated with sweetening agents, such as glycerol, sorbitol or sucrose. Such formulations may also contain a
10 demulcent, a preservative, a flavoring or a coloring agent.

The pharmaceutical compositions of the invention may be in the form of a sterile injectable preparation, such as a sterile injectable aqueous or oleaginous suspension. This suspension may be formulated according to the known art using those suitable dispersing or wetting agents and suspending agents which have been mentioned above. The sterile injectable
15 preparation may also be a sterile injectable solution or suspension in a non-toxic parenterally acceptable diluent or solvent, such as a solution in 1,3-butane-diol or prepared as a lyophilized powder. Among the acceptable vehicles and solvents that may be employed are water, Ringer's solution and isotonic sodium chloride solution. In addition, sterile fixed oils may conventionally be employed as a solvent or suspending medium. For this purpose any bland fixed oil may be
20 employed including synthetic mono- or diglycerides. In addition, fatty acids such as oleic acid may likewise be used in the preparation of injectables.

The amount of active ingredient that may be combined with the carrier material to produce a single dosage form will vary depending upon the host treated and the particular mode of administration. For example, a time-release formulation intended for oral administration to
25 humans may contain approximately 1 to 1000 mg of active material compounded with an appropriate and convenient amount of carrier material which may vary from about 5 to about 95% of the total compositions (weight:weight). The pharmaceutical composition can be prepared to provide easily measurable amounts for administration. For example, an aqueous solution intended for intravenous infusion may contain from about 3 to 500 μ g of the active
30 ingredient per milliliter of solution in order that infusion of a suitable volume at a rate of about 30 mL/hr can occur.

Formulations suitable for administration to the eye include eye drops wherein the active ingredient is dissolved or suspended in a suitable carrier, especially an aqueous solvent for the

active ingredient. The active ingredient is preferably present in such formulations in a concentration of 0.5 to 20%, advantageously 0.5 to 10% particularly about 1.5% w/w.

Formulations suitable for topical administration in the mouth include lozenges comprising the active ingredient in a flavored basis, usually sucrose and acacia or tragacanth; 5 pastilles comprising the active ingredient in an inert basis such as gelatin and glycerin, or sucrose and acacia; and mouthwashes comprising the active ingredient in a suitable liquid carrier.

Formulations for rectal administration may be presented as a suppository with a suitable base comprising for example cocoa butter or a salicylate.

10 Formulations suitable for intrapulmonary or nasal administration have a particle size for example in the range of 0.1 to 500 microns (including particle sizes in a range between 0.1 and 500 microns in increments microns such as 0.5, 1, 30 microns, 35 microns, etc.), which is administered by rapid inhalation through the nasal passage or by inhalation through the mouth so as to reach the alveolar sacs. Suitable formulations include aqueous or oily solutions of the 15 active ingredient. Formulations suitable for aerosol or dry powder administration may be prepared according to conventional methods and may be delivered with other therapeutic agents.

Formulations suitable for vaginal administration may be presented as pessaries, tampons, creams, gels, pastes, foams or spray formulations containing in addition to the active ingredient such carriers as are known in the art to be appropriate.

20 Formulations suitable for parenteral administration include aqueous and non-aqueous sterile injection solutions which may contain anti-oxidants, buffers, bacteriostats and solutes which render the formulation isotonic with the blood of the intended recipient; and aqueous and non-aqueous sterile suspensions which may include suspending agents and thickening agents.

The formulations are presented in unit-dose or multi-dose containers, for example sealed 25 ampoules and vials, and may be stored in a freeze-dried (lyophilized) condition requiring only the addition of the sterile liquid carrier, for example water for injection, immediately prior to use. Extemporaneous injection solutions and suspensions are prepared from sterile powders, granules and tablets of the kind previously described. Preferred unit dosage formulations are those containing a daily dose or unit daily sub-dose, as herein above recited, or an appropriate 30 fraction thereof, of the active ingredient.

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.

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

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.

Compounds of the invention can also be formulated to provide controlled release of the active ingredient to allow less frequent dosing or to improve the pharmacokinetic or toxicity profile of the active ingredient. Accordingly, the invention also provides compositions comprising one or more compounds of the invention formulated for sustained or controlled release.

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

One or more compounds of the invention (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 of this invention is that they are orally bioavailable and can be dosed orally.

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

Test A: Antiviral assay in MT4 Cells

For the antiviral assay, 40 μ L of 1X 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 μ L of virus/cell mixture (2000 cells) was immediately

added to each well containing 40 μ L of diluted compound. The plates were then incubated at 37°C for 5 days. After 5 days of incubation, 25 μ l of 2X concentrated CellTiter-GloTM Reagent (catalog # G7571, Promega Biosciences, Inc., Madison, WI) 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 2 μ M drug concentration is shown in the table below.

10 Test B: Cytotoxicity assay

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.

Compounds of the present invention demonstrate antiviral activity as depicted in the table below. Accordingly, the compounds of the invention may be useful for treating an HIV virus infection, treating AIDS or for delaying the onset of AIDS or ARC symptoms. Shown below are the corresponding values for CC50 and percent inhibition of virus-induced cell killing in the presence of 2 μ M drug concentration.

Compound	%inhibition at 2 μ M	CC50 (nM)
1D	17	30766
2	29	14001
3	40	21900
4	69	10299
5	76	32736
6	45	11424
7	18	17620
8	20	15707
9E	0	35914
10	0	12973
11	0	35671
12	0	8978
13G	97	25557
14	76	25450
15	0	28235
16	0	14004
17	70	13779
18	0	14595
19	25	14241
20	84	48268
21	28	15531
22	0	45696

23	0	13820
24	39	24822
25	71	11920
26	70	24504
27	72	11952
28	93	25972
29	36	13232
30	76	11932
31	34	8633
32	94	19310
33	75	9750
34E	0	27812
35G	49	22398
36F	15	7201
36G	0	6931
37	84	34204
38D	3	42570
38E	86	28602
39	99	>47993
40	99	>48902
41	97	>53000
42	96	>53000
43	28	>53000
44	96	>52456
45	32	>53000
46	87	>53000
47	59	>53000
48	74	>53000
49	0	562
50D	106	16937
51	52	>53000
52	92	13348
53	33	28268
54G	111	10343
55F	101	21646
56B	4	18889
57B	98	13318
58D	14	9996
59E	75	45084
60H	97	23982
61F	74	17882
62	80	9984
63	22	14800
64	88	21071
65	33	11125
66	-2	16799
67	0	6458
68B	28	>53192
69	84	6687
70	56	51249
71	64	>53192
72	56	16153

73	15	9794
74D	4	8470
75	17	10749
76	20	11515
77	65	12434
78	11	7890
79F	19	>50627
80	0	>53192
81D	75	16742
82	114	19283
83	92	25486
84	18	9046
85	9	43043
86	97	21450
87	101	21647
88E	44	>53192
89	73	10675
90F	13	34585
91B	17	22046
92	0	10286
93B	0	8141
94	3	42048
95C	14	14620
96	104	9625
97	27	33870
98	13	17954
99	0	>53192
100	56	7828
101	29	12626
102D	50	21484
103	0	5170
104	32	15722
105	99	9084
107E	30	42789
108	13	>53000
109	50	9085
110	6	7611
111	41	9946
112B	28	>53192
113	78	22275
114	32	>53192
116	72	>53192
117	89	8256
118	108	35951
119	48	>53192
120	73	13828
121	68	9103
122G	101	19919
123E	84	>53192
124C	77	20162
125	0	>53000
126	7	>53000

127C	97	31894
128	7	23549
129	0	10152
130D	39	15764
131C	47	10412
132	7	22253
133	1	>53000
134	98	25170
135	53	21069
136D	88	27842
137	1	21734
138	30	24507
139	8	13954
140	0	>53000
141G	4	21761
142C	23	>53192
143	10	19885
144	89	>53000
145	0	22394
146	66	20592
147	10	>53192
148	11	12278
149	2	>53192
150	15	18420
151E	11	20301
152D	81	28392
153	10	17285
154	90	36786
155	97	36975
156	30	39244
157	10	38312
158	0	8496
159	84	19108
160	45	29334
161	0	9307
162E	37	>53192
163C	105	27367
164	2	29860
165	0	52527
166	0	6358
167	0	>53000
168B	21	11089
169E	94	19777
170C	22	>53192
171	4	11916
172D	104	22084
173	94	25452
174	71	20003
175	1	>53000
176C	59	46532
177	0	51738
178	0	>53000

179C	52	22309
180	93	>50359
181E	99	27266
182	8	50969
183	0	35204
184	5	43151
185C	94	26547
186	80	16844
187	31	18854
188	0	>53000
189D	48	23338
190E	0	25337
191	19	>50905
192	2	47551
193	2	>53192
194	11	>53192
195	85	23013
196	2	29560
197	0	>53192
198	112	45902
199E	18	9517
200B	0	>53192
201	8	>53192
202	1	>53192
203D	0	>53192
204	1	>53192
205	12	13110
206	54	20028
207C	16	13158
208D	2	>53192
209	51	>53192
210	0	>53192
211C	83	36086
212	69	>53192
213C	14	15905
214	8	22180
215	80	19235
216	86	18650
217	92	29562
218	0	>53192
219	1	>53192
220B	70	39195
221	1	40533
222B	21	25598
223	76	41755
224	17	20360
225	15	23007
226C	0	>53000
227	1	14284
228B	51	23388
229	95	18604
230	66	13981

231	79	43226
232	61	18655
233B	5	32173
234	73	15892
235	12	>53192
236D	15	25638
237	1	38182
238E	12	16978
239	18	19379
240C	0	34872
241D	78	25386
242D	97	25477
243	33	>53192
244B	0	16370
245F	71	30316
246	1	47945
247	39	26251
248	88	26502
249	100	23353
250	19	18457
251	1	>53192
252	18	19227
253	27	>53192
254	91	16562
255	1	>53192
256	15	>53192
257	7	>53192
258	8	>53192
259	2	47617
260	54	28136
261	6	21226
262G	109	>51193
263	17	>53192
264	24	>53192
265	74	>53192
266C	0	51915
267	5	>52894
268	27	27745
269	8	>53192
270C	1	>53192
271B	15	11411
272F	92	14257
273	10	29555
274	0	11007
275	53	16906
276	29	16948
277B	96	19304
278	121	8534
279G	82	9300
280	0	4177
281C	5	28296
282	0	>53192

283C	65	24368
284	50	16234
285G	58	48534
286	0	25178
287E	98	15976
288	108	16448
289	2	26418
290	4	11503
291	86	16519
292	1	>53192
293	44	11190
294	114	20456
295B	99	>53192
296	96	10826
297	14	23313
298C	61	>53000
299D	100	19498
300	0	>53192
301B	0	5652
302	0	16805
303	14	35540
304C	94	1699
305	0	>53192
306C	10	41624
307	99	26681
308	102	39781
309	9	12000
310C	97	>53000
311B	97	14846
312	2	>53192
313	14	>53192
314	3	23595
315	0	47185
316	100	21369
317	41	>47618
318	27	>53192
319	70	>52484
320	110	12474
321	30	29687
322	10	37130
323	0	>53192
324	31	>53192
325	86	46137
326	27	>53192
327	94	>53192
328	0	10002
329	99	14697
330	3	29347
331B	99	43107
332B	2	39967
333	2	>53192
334	63	26549

335	3	51148
336	0	>53192
337	20	27878
338C	35	>53000
339B	53	19437
340B	32	32752
341	13	26585
342C	119	13655
343	62	15548
344	93	17232
345	21	12409
346D	1	39020
347	1	19378
348	103	14152
349B	94	40798
350	10	28062
351	95	8601
352	16	32910
353B	110	12655
354	82	>53000
355	1	9465
356	76	20617
357	0	8824
358	20	47446
359	2	25272
360E	55	13132
361	8	>53192
362	23	>53000
363	2	21873
364	38	3757
365	86	12470
366	6	>53192
367	20	13404
368	2	47287
369	5	>53000
370	33	22663
371	83	7589
372	0	24037
373	0	8142
374	5	>53192
375	98	15176
376	2	29126
377	22	18646
378	5	17140
379	112	9237
380	97	18292
381	1	24923
382	85	>39934
383	32	15504
384	97	>53192
385	40	>53192
386	114	11949

387	61	21235
388	54	>53192
389B	2	>53192
390	99	21565
391	60	44809
392	105	19144
393	54	26117
394	14	30759
395	41	11615
396	39	9999
397	26	>53192
398	2	9831
399	31	12770
400	45	23303
401C	87	9717
402	92	24761
403	112	10455
404	0	44624
405	11	21128
406	27	11432
407	102	11978
408	88	12745
409	0	>53192
410	103	13729
411	53	8978
412	80	11140
413	61	14499
414	39	23433
415	39	38002
416	0	10281
417	8	12778
418	19	>53192
419	42	27120
420	110	18698
421	70	10198
422	0	6763
423	14	8455
424	78	14163
425	85	15596
426	19	>53000
427	0	32797
428	94	23043
429	57	41551
430	31	26293
431	7	6387
432	90	7993
433	16	20821
434	20	12326
435	7	13856
436	20	11275
437	3	>53192
438	81	12103

439	-2	21696
440	82	21699
441	35	8649
442	79	8876
443I	82	16399
444	23	15522
445	114	10720
446	79	>53192
447	0	12969
448	103	>53192
449	94	21114
450	33	19264
451B	1	37054
452C	4	9069
453	3	>53192
454	1	11111
455	4	>53192
456	0	>53192
457	64	>53192
458	90	15703
459	28	14198
460	0	8970
461	25	32036
462J	2	17992
463	11	14737
464	119	>53192
465B	3	>53192
466	115	>53192
467	103	>53192
468D	14	>53000
469	17	>53192
470	68	20769
471	62	>53192
473	18	14644
474	17	9979
475	23	20371
476	30	53182
477	0	21395
478E	0	21514
479	2	26449
480	93	27787
481	53	22927
482C	2	51352
483D	19	26191
484	25	27390
485	43	22202
486	76	7076
487C	10	9712
488	8	12411
489D	97	20784
490D	87	38047
491F	18	7849

492B	2	>53192
493	48	33923
494	17	10354
495	85	15531
496B	17	18411
497	67	27052
498F	60	13214
499	22	>53000
500	59	24349
501	11	39631
502F	50	3054
503	3	40356
504E	142	12820
505	28	>47368
506	32	>53000
507B	22	>45266
508D	96	5132
509	48	24601
510	3	35940
511C	17	11777
512C	60	19883
513	63	10682
514	3	>46077
515	0	9461
517E	87	19079
518	11	10548
519	65	20324
520	30	>53192
521	0	>53192
522	4	47889
523	24	48801
524D	78	8533
525	83	>53192
526	50	10031
527E	66	10638
528	0	>53192
529	53	13001
530E	55	15251
531	98	7401
532	9	12162
533E	142	19292
534	29	9824
535G	9	25309
536I	12	8605
537	2	>53192
538	14	23328
539	10	20785
540E	-4	>53192
541	37	8152
542	1	33639
543	4	43954
544	75	>53192

545	37	15894
546C	15	16774
547	45	13332
548D	54	10129
549	38	10166
550	1	16979
551	0	>53192
552	8	11041
553	11	23837
554	63	48909
555C	14	25510
556	83	47803
557	73	7859
558B	3	>53192
559D	96	23060
560	112	>53000
561B	8	29040
562	42	17783
563	62	27019
564	100	10281
565	0	37625
566	3	23700
567	11	15782
568	42	11417
569	11	>53000
570	5	>53192
571	2	34848
572B	11	36737
573	18	30054
574D	24	52462
575B	14	17450
576B	2	>53192
577	20	>53192
578	15	>53192
579D	18	>53192
580F	95	32553
581D	6	10563
582	5	14430
583	28	23239
584	93	7251
585	58	13736
586	1	>53192
587C	93	22970
588	2	21529
589	106	17933
590	13	38595
591	15	14237
592	8	>53192
593	52	>53000
594B	12	13423
595	99	12699
596	96	10945

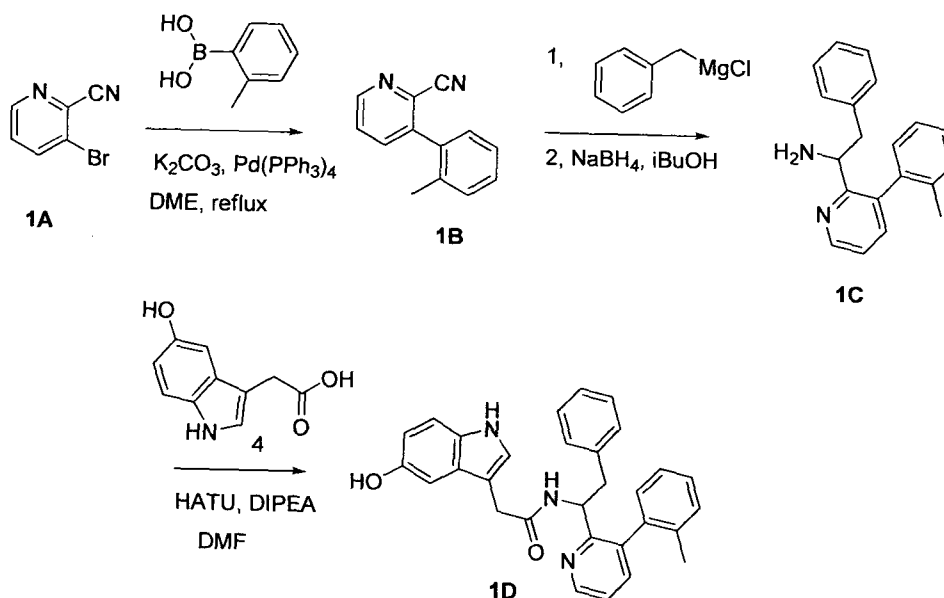
597	89	8650
598	3	>53192
599	2	31550
600	9	>53192
601	22	41944

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.

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.

The invention will now be illustrated by the following non-limiting Examples. The Examples provided herein describe the synthesis of compounds of the invention (i.e. compounds of Formula I) as well as intermediates used to prepare compounds of the invention.

Example 1



Synthesis of 3-o-tolylpicolinonitrile(1B):

To a suspension of 3-bromopicolinonitrile (1.0g, 5.46 mmol), potassium carbonate (27ml, 0.4M in water), o-tolylboronic acid (**1A**, 0.74g, 5.46 mmol) and tetrakis(triphenylphosphine) palladium (310 mg, 0.27 mmol) in DME (40 ml), was degassed for 20 minutes. The mixture was then heated at reflux. After 2 hours the reaction was filtered through celite and the filtrate was extracted with EtOAc (30 ml) twice. The organic layer was dried over Na₂SO₄, filtered and concentrated. The crude product was purified by flash column (Rf: 0.3 EtOAc/Hexanes = 20%). The yield was 94%. MS (*m/z*) 195 [M+H]⁺

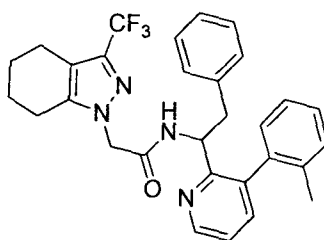
Synthesis of 2-phenyl-1-(3-o-tolylpyridin-2-yl)ethanamine (**1C**):

To a solution of 3-o-tolylpicolinonitrile (0.5 g, 2.56 mmol) in toluene cooled by an ice bath, benzylmagnesium chloride (2M in THF) (3.0 ml, 6.0mmol) was added dropwise. After 30 minutes, the reaction was warmed up to room temperature and stirring was continued for 1 hr. The reaction was then cooled to 0°C and 2-butanol (10 ml) was added. NaBH₄ (187 mg, 4.93 mmol) was then added to the solution and the reaction was stirred overnight (warmed up to r.t. slowly). The reaction was quenched with MeOH(3 ml) and extracted with EtOAc (2x30 ml). The organic layer was dried with Na₂SO₄, filtered and concentrated. The crude product was purified by flash column. The yield was (180 mg, 0.62 mmol) 24.2%. MS (*m/z*) 289 [M+H]⁺

Synthesis of 2-(6-hydroxy-1H-indol-3-yl)-N-(2-phenyl-1-(3-o-tolylpyridin-2-yl)ethyl)acetamide (**1D**):

HATU (40 mg, 0.105 mmol) was added to a solution of 2-(5-hydroxy-1H-indol-3-yl)acetic acid (19.2 mg, 0.1mmol) and DIPEA (0.02ml, 0.12 mmol) in DMF (0.3 ml). After 10 minutes, 2-phenyl-1-(3-o-tolylpyridin-2-yl)ethanamine (29 mg, 0.1 mmol) in 0.2 ml of DMF was added to the reaction. The reaction was stirred for 2 hours. The DMF solution was filtered and purified by RP HPLC to provide the desired product. The yield was 24 mg. The product is a mixture of rotamers. The ratio is 3:2. NMR of the major rotamer is reported. ¹H NMR (*d*-DMSO, 400 MHz) δ 10.22 (s, 1H), 8.6-8.62 (m, 1H), 8.05 (d, 1H), 7.45 (d, 1H), 7.34-7.4 (m, 1H), 7.2-7.31 (m, 2H), 7.0-7.18 (m, 5H), 6.88 (s, 1H), 6.75 (s, 1H), 6.0-6.64 (m, 2H), 6.5-6.58 (m, 2H), 4.75 (q, 1H), 3.3-3.41 (m, 2H), 2.7-2.9 (m, 2H), 1.92 (s, 3H); MS (*m/z*) 462 [M+H]⁺.

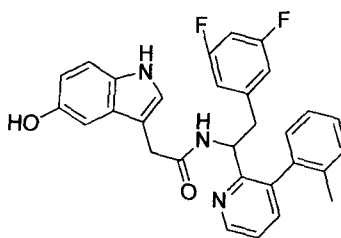
Example 2

**2**

Synthesis of N-(2-phenyl-1-(3-(o-tolyl)pyridin-2-yl)ethyl)-2-(3-(trifluoromethyl)-4,5,6,7-tetrahydro-1H-indazol-1-yl)acetamide (**2**):

The title compound was prepared according to the method presented for the synthesis of Compound 1D of Example 1 substituting 2-(3-(trifluoromethyl)-4,5,6,7-tetrahydro-1H-indazol-1-yl)acetic acid for 2-(5-hydroxy-1H-indol-3-yl)acetic acid. MS (*m/z*) 519 [M+H]⁺.

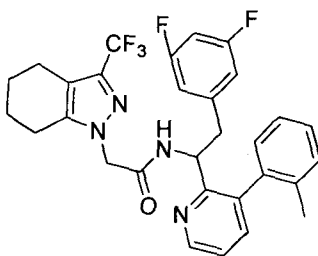
Example 3

**3**

The synthesis of N-(2-(3,5-difluorophenyl)-1-(3-o-tolylpyridin-2-yl)ethyl)-2-(5-hydroxy-1H-indol-3-yl)acetamide (**3**):

The title compound was prepared according to the method presented for the synthesis of Compound 1D of Example 1 substituting (3,5-difluorobenzyl)magnesium chloride for benzylmagnesium chloride. MS (*m/z*) 498 [M+H]⁺.

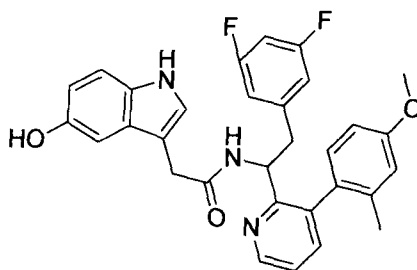
Example 4

**4**

The synthesis of N-(2-(3,5-difluorophenyl)-1-(3-o-tolylpyridin-2-yl)ethyl)-2-(3-(trifluoromethyl)-4,5,6,7-tetrahydro-1H-indazol-1-yl)acetamide (4):

The title compound was prepared according to the method presented for the synthesis of Compound 1D of Example 1 substituting (3,5-difluorobenzyl)magnesium chloride for benzylmagnesium chloride and 2-(3-(trifluoromethyl)-4,5,6,7-tetrahydro-1H-indazol-1-yl)acetic acid for 2-(5-hydroxy-1H-indol-3-yl)acetic acid. MS (m/z) 555 $[M+H]^+$.

Example 5

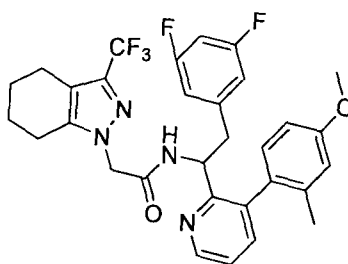


5

The synthesis of N-(2-(3,5-difluorophenyl)-1-(3-(4-methoxy-2-methylphenyl)pyridin-2-yl)ethyl)-2-(5-hydroxy-1H-indol-3-yl)acetamide (5):

The title compound was prepared according to the method presented for the synthesis of Compound 1D of Example 1 substituting 4-methoxy-2-methylphenylboronic acid for o-tolylboronic acid and (3,5-difluorobenzyl)magnesium chloride for benzylmagnesium chloride to provide. MS (m/z) 528 $[M+H]^+$.

Example 6



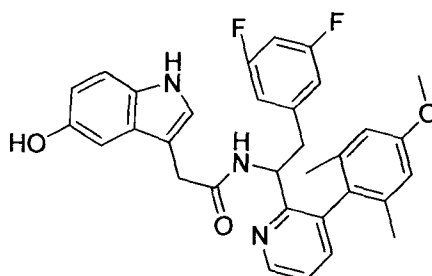
6

The synthesis of N-(2-(3,5-difluorophenyl)-1-(3-(4-methoxy-2-methylphenyl)pyridin-2-yl)ethyl)-2-(3-(trifluoromethyl)-4,5,6,7-tetrahydro-1H-indazol-1-yl)acetamide (6):

The title compound was prepared according to the method presented for the synthesis of Compound 1D of Example 1 substituting 4-methoxy-2-methylphenylboronic acid for o-

tolylboronic acid, (3,5-difluorobenzyl)magnesium chloride for benzylmagnesium chloride, and 2-(3-(trifluoromethyl)-4,5,6,7-tetrahydro-1H-indazol-1-yl)acetic acid for 2-(5-hydroxy-1H-indol-3-yl)acetic acid. MS (m/z) 585 $[M+H]^+$.

5 Example 7

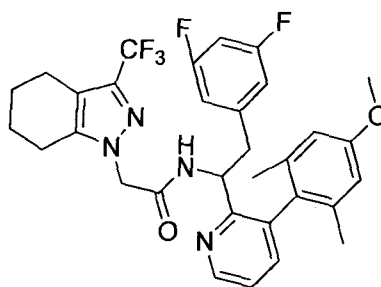


7

The synthesis of N-(2-(3,5-difluorophenyl)-1-(3-(4-methoxy-2,6-dimethylphenyl)pyridin-2-yl)ethyl)-2-(5-hydroxy-1H-indol-3-yl)acetamide (7):

The title compound was prepared according to the method presented for the synthesis of Compound 1D of Example 1 substituting 4-methoxy-2,6-dimethylphenylboronic acid for o-tolylboronic acid and (3,5-difluorobenzyl)magnesium chloride for benzylmagnesium chloride. MS (m/z) 542 $[M+H]^+$.

Example 8

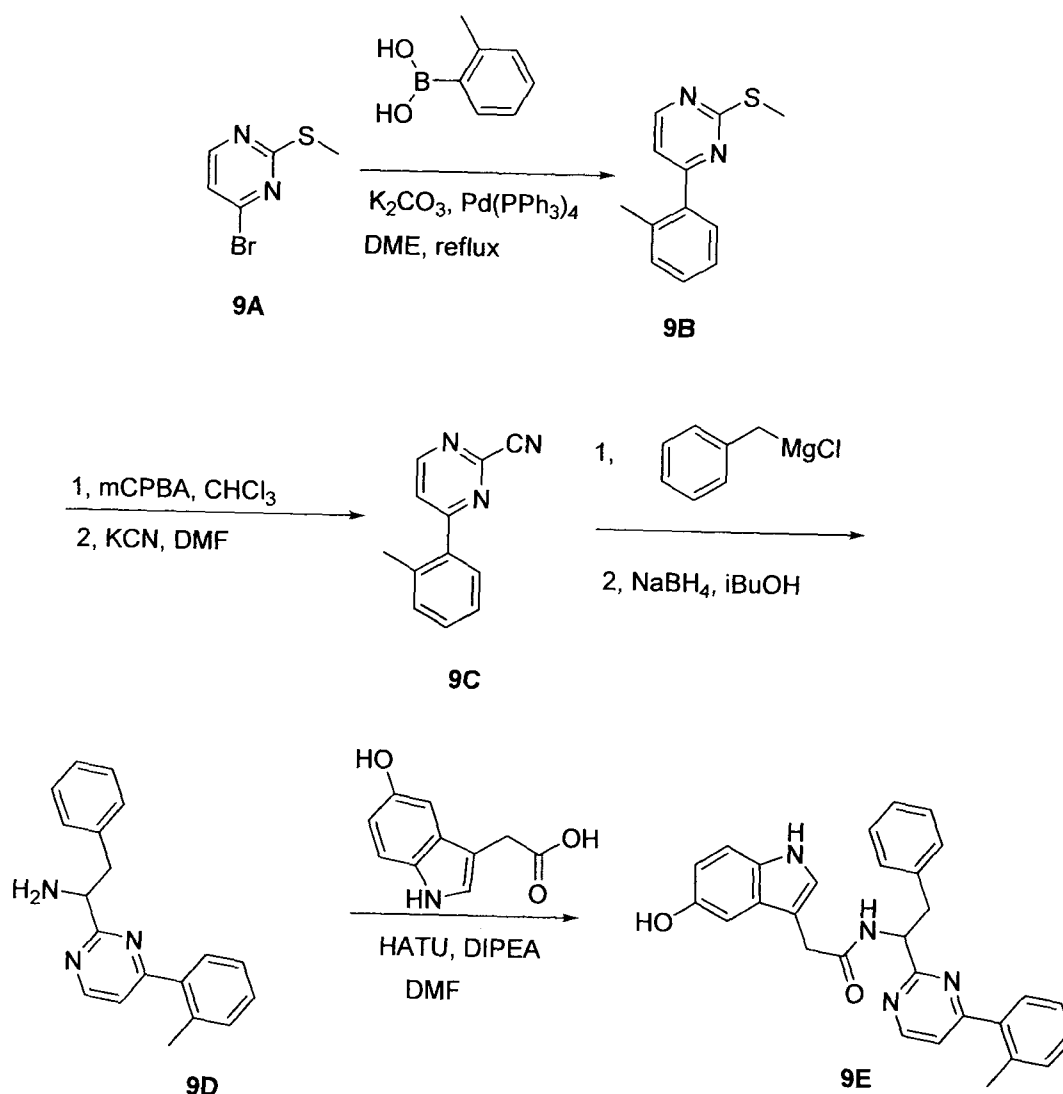


8

The synthesis of N-(2-(3,5-difluorophenyl)-1-(3-(4-methoxy-2,6-dimethylphenyl)pyridin-2-yl)ethyl)-2-(3-(trifluoromethyl)-4,5,6,7-tetrahydro-1H-indazol-1-yl)acetamide (8):

The title compound was prepared according to the method presented for the synthesis of Compound 1D of Example 1 substituting 4-methoxy-2,6-dimethylphenylboronic acid for o-tolylboronic acid, (3,5-difluorobenzyl)magnesium chloride for benzylmagnesium chloride, and 2-(3-(trifluoromethyl)-4,5,6,7-tetrahydro-1H-indazol-1-yl)acetic acid for 2-(5-hydroxy-1H-indol-3-yl)acetic acid. MS (m/z) 599 $[M+H]^+$.

Example 9

Synthesis of 2-(methylthio)-4-o-tolylpyrimidine (**9B**):

- 5 A suspension of 4-bromo-2-(methylthio)pyrimidine (**9A**, 1.18g, 7.35 mmol), potassium carbonate (37ml, 0.4 M in water), o-tolylboronic acid (1 g, 7.35 mmol) and tetrakis(triphenylphosphine)palladium(0) (425 mg, 0.37 mmol) in DME (40 ml) was degassed for 20 minutes. It was then heated at reflux for 2 hours. The reaction mixture was cooled and filtered through celite. The filtrate was extracted with EtOAc (2 x 30 ml). The organic layer was
- 10 dried with Na_2SO_4 , filtered and concentrated. The crude product was purified by flash column (Rf: 0.3 10%EtOAc/Hexanes). The yield was 98%. MS (m/z) 217 [$M+H$] $^+$

Synthesis of 4-o-tolylpyrimidine-2-carbonitrile (**9C**):

- 15 To a solution of 2-(methylthio)-4-o-tolylpyrimidine (1.55g, 7.2 mmol) in DCM (10 ml) was added mCPBA (77% from Aldrich) (1.25 g, 5.6 mmol). The reaction mixture was stirred for 2

hours then diluted with DCM (50 ml) and washed with NaHCO₃(aq) (2x50 ml). The organic layer was dried over Na₂SO₄, filtered and concentrated. The crude product was dried under high vacuum then redissolved in DMF. KCN(s) (936 mg, 14.4mmol) was added to the solution and the reaction was stirred overnight. The reaction was diluted with EtOAc (100 ml) and washed with NaHCO₃(aq) (2x50 ml). The organic layer was dried over Na₂SO₄, filtered and concentrated. The crude product was purified by flash column (Rf: 0.3 EtOAc/Hexanes = 15%). The yield was (690 mg, 3.53 mmol). 49% for two steps. MS (*m/z*) 196 [M+H]⁺

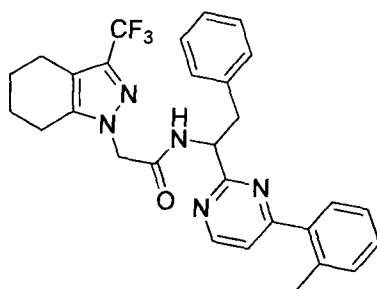
Synthesis of 2-phenyl-1-(4-o-tolylpyrimidin-2-yl)ethanamine (**9D**):

Benzylmagnesium chloride (2M in THF) (2.11 ml, 4.22 mmol) was added dropwise to a solution of 4-o-tolylpyrimidine-2-carbonitrile (9C, 690 mg, 3.52 mmol) in toluene (10 ml) at 0 °C. After 30 minutes, the reaction was warmed up to r.t. and stirred for 1 hr. The reaction was then cooled it to 0 °C and 2-butanol (10 ml) was added followed by NaBH₄(s) (187 mg, 4.93 mmol). The reaction mixture was stirred overnight at room temperature. The reaction was quenched with MeOH (3 ml) and extracted with EtOAc (2x30 ml). The organic layer was dried with Na₂SO₄, filtered and concentrated. The crude product was purified by flash column (Rf: 0.4 10%MeOH/DCM). The yield was 380. MS (*m/z*) 290 [M+H]⁺

Synthesis of 2-(5-hydroxy-1H-indol-3-yl)-N-(2-phenyl-1-(4-o-tolylpyrimidin-2-yl)ethyl)acetamide (**9E**):

HATU (40 mg, 0.105 mmol) was added to a solution of 2-(5-hydroxy-1H-indol-3-yl)acetic acid (19.2 mg, 0.1mmol) and DIEPA (0.02ml, 0.12 mmol) in DMF (0.3 ml). After 10 minutes, 2-phenyl-1-(4-o-tolylpyrimidin-2-yl)ethanamine (29 mg, 0.1 mmol) in 0.2 ml of DMF was added to the reaction. The reaction was stirred for 2 hours. 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/ H₂O, B=0.1% TFA/acetonitrile) to provide the title compound. The yield was 30 mg. ¹H NMR (*d*-DMSO, 400 MHz) δ 10.48 (s, 1H), 8.79 (d, 1H), 8.14 (d, 1H), 7.5 (d, 1H), 7.22-7.3 (m, 4H), 7.08-7.35 (m, 4H), 6.92-6.98 (m, 3H), 6.6 (s, 1H), 6.58 (d, 1H), 5.21 (q, 1H), 3.4-3.55 (m, 2H), 3.0-3.2 (m, 2H), 1.98 (s, 3H); MS (*m/z*) 463 [M+H]⁺

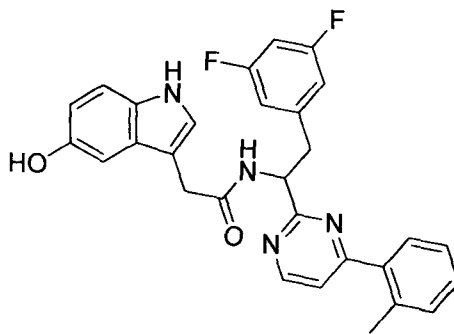
Example 10

**10**

The synthesis of N-(2-phenyl-1-(4-o-tolylpyrimidin-2-yl)ethyl)-2-(3-(trifluoromethyl)-4,5,6,7-tetrahydro-1H-indazol-1-yl)acetamide (**10**):

The title compound was prepared according to the method presented in the synthesis of Example 9 substituting 2-(3-(trifluoromethyl)-4,5,6,7-tetrahydro-1H-indazol-1-yl)acetic acid for 2-(5-hydroxy-1H-indol-3-yl)acetic acid. MS (m/z) 520 $[M+H]^+$.

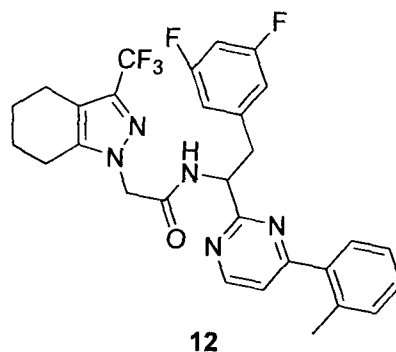
Example 11

**11**

The synthesis of N-(2-(3,5-difluorophenyl)-1-(4-o-tolylpyrimidin-2-yl)ethyl)-2-(5-hydroxy-1H-indol-3-yl)acetamide (**11**):

The title compound was prepared according to the method presented in the synthesis of Example 9 substituting (3,5-difluorobenzyl)magnesium chloride for benzylmagnesium chloride. MS (m/z) 499 $[M+H]^+$.

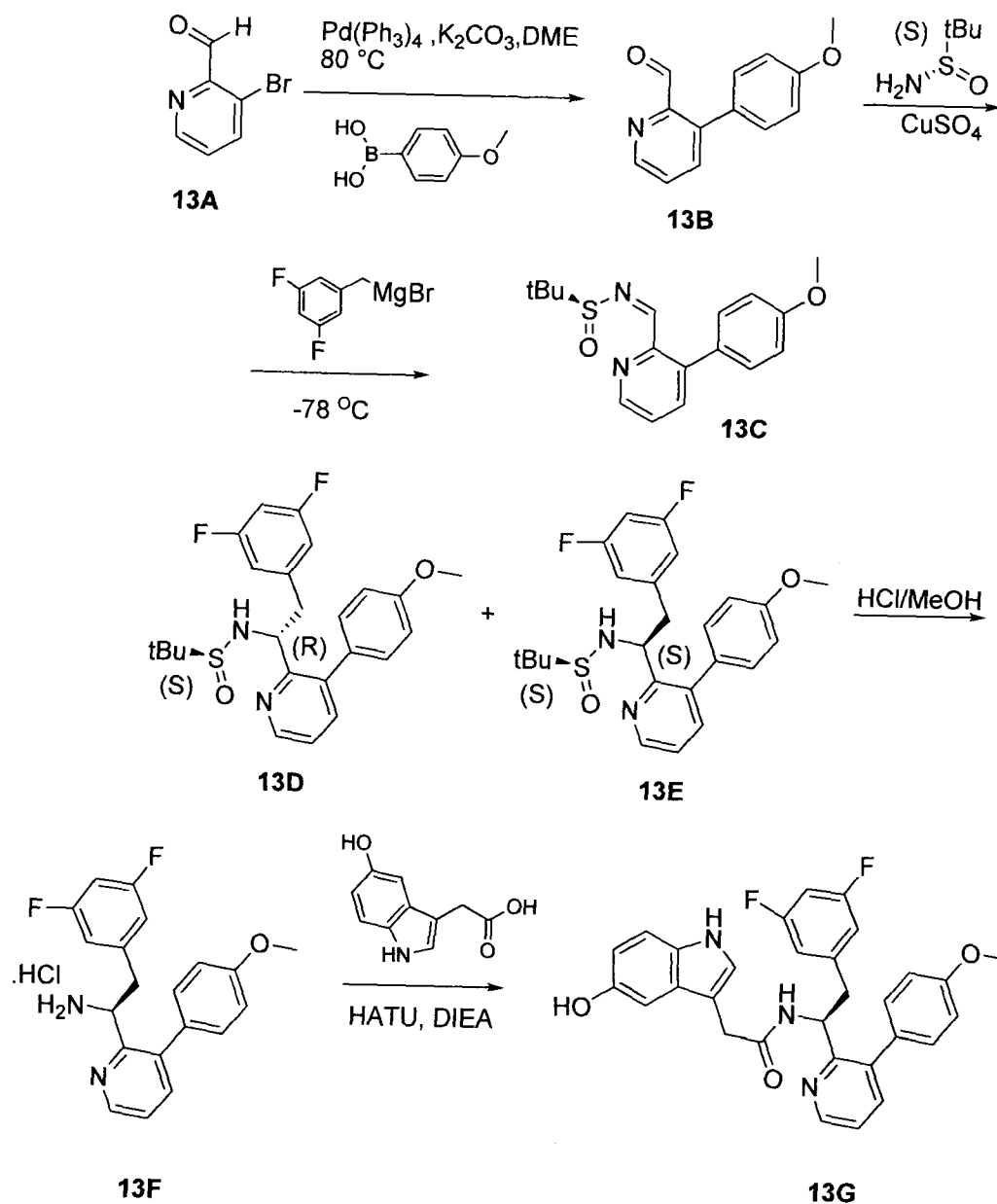
Example 12



The synthesis of N-(2-(3,5-difluorophenyl)-1-(4-o-tolylpyrimidin-2-yl)ethyl)-2-(3-(trifluoromethyl)-4,5,6,7-tetrahydro-1H-indazol-1-yl)acetamide (**12**):

5 The title compound was prepared according to the method presented in the synthesis of Example 9 substituting (3,5-difluorobenzyl)magnesium chloride for benzylmagnesium chloride and 2-(3-(trifluoromethyl)-4,5,6,7-tetrahydro-1H-indazol-1-yl)acetic acid for 2-(5-hydroxy-1H-indol-3-yl)acetic acid. MS (m/z) 556 $[M+H]^+$.

Example 13



Synthesis of 3-(4-methoxyphenyl)picolinaldehyde (**13B**):

A suspension of 3-bromopicolinaldehyde (**13A**, 1.86 g, 10 mmol), potassium carbonate (50ml, 2M in water), 4-methoxyphenylboronic acid (1.6g, 10.5 mmol) and tetrakis(triphenylphosphine) palladium (580 mg, 0.5 mmol) in DME (70 ml) was degassed for 30 minutes. The mixture was heated at reflux for 2 hours. The reaction was cooled and filtered through celite. The filtrate was extracted with EtOAc (2x50 ml). The organic layer was dried over Na_2SO_4 , filtered and concentrated. The crude product was purified by flash column (Rf: 0.4 50 % EtOAc/Hexanes). The yield was 2g. MS (m/z) 214 [$\text{M}+\text{H}$]⁺

Synthesis of (S)-N-((3-(4-methoxyphenyl)pyridin-2-yl)methylene)-2-methylpropane-2-sulfonamide (**13C**):

Copper(II) sulfate (anhydrous 2.52 g, 17.2 mmol) was added to a solution of 3-(4-methoxyphenyl)picolinaldehyde (1.7 g, 8.6 mmol) and (S)-2-methylpropane-2-sulfinamide (1.06 g, 9.4 mmol) in DCM (20 ml). The suspension was stirred overnight at room temperature. The reaction was filtered and washed with DCM (3x20 ml). The filtrate was concentrated. The crude product was purified by flash column (Rf: 0.6, 60% EtOAc/ Hexanes). The yield was (2.4 g, 7.7 mmol) 90%. MS (*m/z*) 195 [*M*+H]⁺

Synthesis of (S)-N-((R)-2-(3,5-difluorophenyl)-1-(3-(4-methoxyphenyl)pyridin-2-yl)ethyl)-2-methylpropane-2-sulfinamide (**13D**) and (S)-N-((S)-2-(3,5-difluorophenyl)-1-(3-(4-methoxyphenyl)pyridin-2-yl)ethyl)-2-methylpropane-2-sulfinamide(**13E**): (3,5-difluorobenzyl)magnesium bromide (0.25 M in ether, 10 ml, 2.5 mmol) was added dropwise to a solution of (S)-N-((3-(4-methoxyphenyl)pyridin-2-yl)methylene)-2-methylpropane-2-sulfinamide (**13C**, 0.5 g, 1.67 mmol) in DCM (40 ml) at – 78 °C. The reaction was stirred for 3 hour at – 78 °C. Ammonium chloride(aq, 10ml) was added to the reaction and the mixture was allowed to warm to r.t. The mixture was extracted with EtOAc (2x30ml). The organic layer was dried over Na₂SO₄, filtered and concentrated. The crude product contained a mixture of diastereomers **13D** ((S,R) sulfinamide intermediate) and **13E** ((S,S) sulfinamide intermediate) separable by flash chromatography (Rf: 0.3 50% EtOAc/Hexanes). The yield was (220 mg, 30%). MS (*m/z*) 445 [*M*+H]⁺

20

(S)-2-(3,5-difluorophenyl)-1-(3-(4-methoxyphenyl)pyridin-2-yl)ethanamine hydrochloride salt (**13F**):

(S)-N-((S)-2-(3,5-difluorophenyl)-1-(3-(4-methoxyphenyl)pyridin-2-yl)ethyl)-2-methylpropane-2-sulfinamide (**13E**, 220 mg, 0.5 mmol) 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. Used without further purification. MS (*m/z*) 341 [*M*+H]⁺

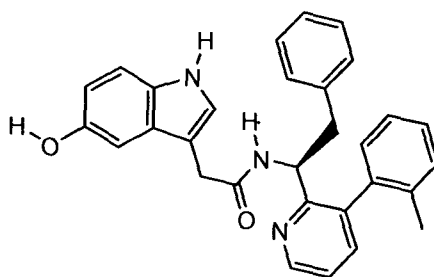
25

Synthesis of (S)-N-(2-(3,5-difluorophenyl)-1-(3-(4-methoxyphenyl)pyridin-2-yl)ethyl)-2-(5-hydroxy-1H-indol-3-yl)acetamide (**13G**):

HATU (40 mg, 0.105 mmol) was added to a solution of 2-(5-hydroxy-1H-indol-3-yl)acetic acid (19.2 mg, 0.1mmol) and DIPEA (0.04ml, 0.24 mmol) in DMF (0.3 ml). After 10 minutes, (S)-2-(3,5-difluorophenyl)-1-(3-(4-methoxyphenyl)pyridin-2-yl)ethanamine hydrochloride salt (34 mg, 0.1 mmol) in 0.2 ml of DMF was added . The reaction was stirred for 2 hours 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/ H₂O, B=0.1% TFA/acetonitrile) to provide the desired product. The yield was 39 mg. ¹H NMR (*d*-DMSO, 400 MHz) δ 10.22 (s, 1H), 8.6 (d, 1H), 8.4 (d, 1H), 7.53 (d, 1H), 7.3-7.4 (m, 1H), 7.0-7.1 (m, 3H), 6.8-6.98 (m, 4H), 6.78 (s, 1H), 6.56 (d, 1H), 6.3-6.4 (m, 2H), 5.21 (q, 1H), 3.75 (s, 3H), 3.4 (s, 2H), 2.9 (d, 2H); MS (*m/z*) 514 [M+H]⁺

Example 14



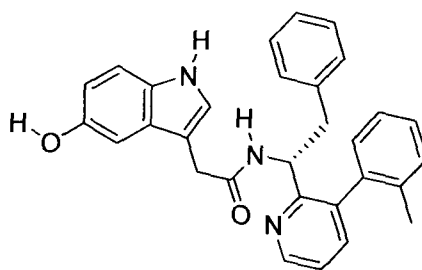
14

- 10 The synthesis of (S)-2-(5-hydroxy-1H-indol-3-yl)-N-(2-phenyl-1-(3-o-tolylpyridin-2-yl)ethyl)acetamide (**14**):

The title compound was prepared according to the method presented in the synthesis of Example 13 substituting *o*-tolylboronic acid for 4-methoxyphenylboronic acid and benzylmagnesium chloride for (3,5-difluorobenzyl)magnesium chloride. MS (*m/z*) 462 [M+H]⁺.

15

Example 15



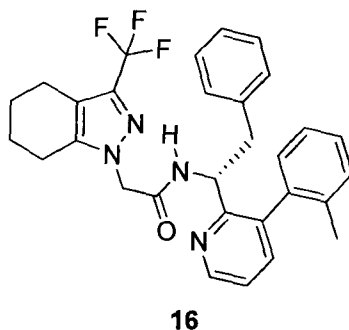
15

The synthesis of (R)-2-(5-hydroxy-1H-indol-3-yl)-N-(2-phenyl-1-(3-o-tolylpyridin-2-yl)ethyl)acetamide (**15**):

- 20 The title compound was prepared according to the method presented in the synthesis of Example 13 substituting *o*-tolylboronic acid for 4-methoxyphenylboronic acid and benzylmagnesium

chloride for (3,5-difluorobenzyl)magnesium chloride and carrying forward the (S,R) sulfinamide intermediate. MS (m/z) 462 $[M+H]^+$.

Example 16

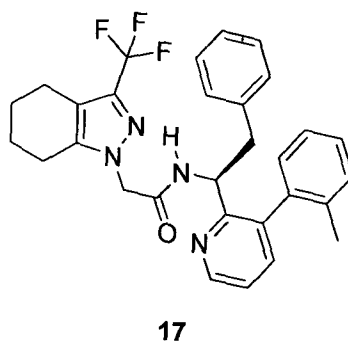


5

The synthesis of (R)-N-(2-phenyl-1-(3-o-tolylpyridin-2-yl)ethyl)-2-(3-(trifluoromethyl)-4,5,6,7-tetrahydro-1H-indazol-1-yl)acetamide (**16**):

The title compound was prepared according to the method presented in the synthesis of Example 13 substituting o-tolylboronic acid for 4-methoxyphenylboronic acid, benzylmagnesium chloride for (3,5-difluorobenzyl)magnesium chloride, 2-(3-(trifluoromethyl)-4,5,6,7-tetrahydro-1H-indazol-1-yl)acetic acid for 2-(5-hydroxy-1H-indol-3-yl)acetic acid and carrying forward the (S,R) sulfinamide intermediate. MS (m/z) 519 $[M+H]^+$.

Example 17

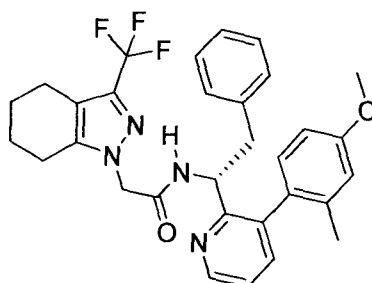


15

The synthesis of (S)-N-(2-phenyl-1-(3-o-tolylpyridin-2-yl)ethyl)-2-(3-(trifluoromethyl)-4,5,6,7-tetrahydro-1H-indazol-1-yl)acetamide (**17**):

The title compound was prepared according to the method presented in the synthesis of Example 13 substituting o-tolylboronic acid for 4-methoxyphenylboronic acid, benzylmagnesium chloride for (3,5-difluorobenzyl)magnesium chloride, and 2-(3-(trifluoromethyl)-4,5,6,7-tetrahydro-1H-indazol-1-yl)acetic acid for 2-(5-hydroxy-1H-indol-3-yl)acetic acid. MS (m/z) 519 $[M+H]^+$.

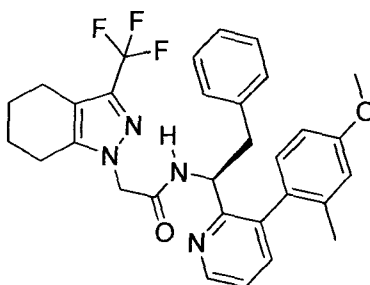
Example 18

**18**

The synthesis of (R)-N-(1-(3-(4-methoxy-2-methylphenyl)pyridin-2-yl)-2-phenylethyl)-2-(3-(trifluoromethyl)-4,5,6,7-tetrahydro-1H-indazol-1-yl)acetamide (**18**):

The title compound was prepared according to the method presented in the synthesis of Example 13 substituting 4-methoxy-2-methylphenylboronic acid for 4-methoxyphenylboronic acid, benzylmagnesium chloride for (3,5-difluorobenzyl)magnesium chloride, 2-(3-(trifluoromethyl)-4,5,6,7-tetrahydro-1H-indazol-1-yl)acetic acid for 2-(5-hydroxy-1H-indol-3-yl)acetic acid and carrying forward the (S,R) sulfinamide intermediate. MS (m/z) 549 $[M+H]^+$.

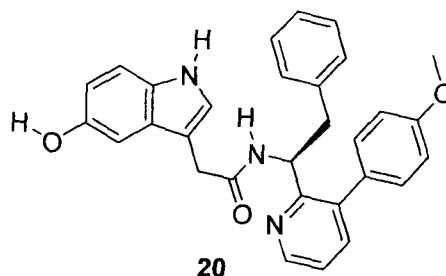
Example 19

**19**

The synthesis of (S)-N-(1-(3-(4-methoxy-2-methylphenyl)pyridin-2-yl)-2-phenylethyl)-2-(3-(trifluoromethyl)-4,5,6,7-tetrahydro-1H-indazol-1-yl)acetamide (**19**):

The title compound was prepared according to the method presented in the synthesis of Example 13 substituting 4-methoxy-2-methylphenylboronic acid for 4-methoxyphenylboronic acid, benzylmagnesium chloride for (3,5-difluorobenzyl)magnesium chloride, and 2-(3-(trifluoromethyl)-4,5,6,7-tetrahydro-1H-indazol-1-yl)acetic acid for 2-(5-hydroxy-1H-indol-3-yl)acetic acid. MS (m/z) 549 $[M+H]^+$.

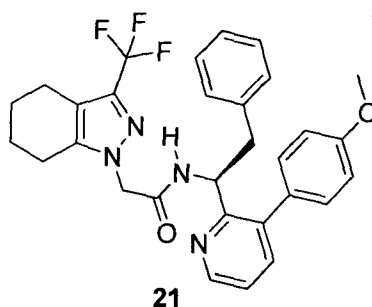
Example 20



The synthesis of (S)-2-(5-hydroxy-1H-indol-3-yl)-N-(1-(3-(4-methoxyphenyl)pyridin-2-yl)-2-phenylethyl)acetamide (**20**):

- 5 The title compound was prepared according to the method presented in the synthesis of Example 13 substituting benzylmagnesium chloride for (3,5-difluorobenzyl)magnesium chloride. MS (m/z) 478 $[M+H]^+$.

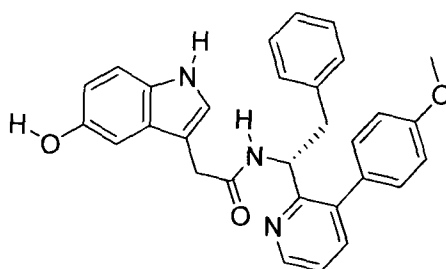
Example 21



10 The synthesis of (S)-N-(1-(3-(4-methoxyphenyl)pyridin-2-yl)-2-phenylethyl)-2-(3-(trifluoromethyl)-4,5,6,7-tetrahydro-1H-indazol-1-yl)acetamide (**21**):

- The title compound was prepared according to the method presented in the synthesis of Example 13 substituting benzylmagnesium chloride for (3,5-difluorobenzyl)magnesium chloride, and 2-
15 (3-(trifluoromethyl)-4,5,6,7-tetrahydro-1H-indazol-1-yl)acetic acid for 2-(5-hydroxy-1H-indol-3-yl)acetic acid. MS (m/z) 535 $[M+H]^+$.

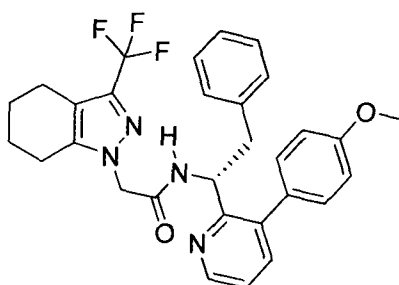
Example 22

**22**

The synthesis of (R)-2-(5-hydroxy-1H-indol-3-yl)-N-(1-(3-(4-methoxyphenyl)pyridin-2-yl)-2-phenylethyl)acetamide (**22**):

The title compound was prepared according to the method presented in the synthesis of Example 13 substituting benzylmagnesium chloride for (3,5-difluorobenzyl)magnesium chloride and carrying forward the (S,R) sulfinamide intermediate. MS (m/z) 478 $[M+H]^+$.

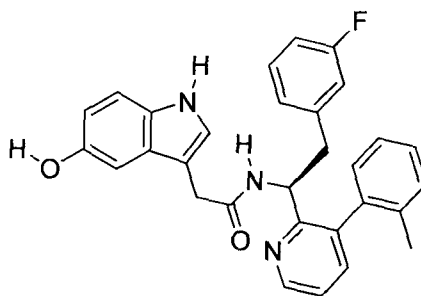
Example 23

**23**

The synthesis of (R)-N-(1-(3-(4-methoxyphenyl)pyridin-2-yl)-2-phenylethyl)-2-(3-(trifluoromethyl)-4,5,6,7-tetrahydro-1H-indazol-1-yl)acetamide (**23**):

The title compound was prepared according to the method presented in the synthesis of Example 13 substituting benzylmagnesium chloride for (3,5-difluorobenzyl)magnesium chloride, 2-(3-(trifluoromethyl)-4,5,6,7-tetrahydro-1H-indazol-1-yl)acetic acid for 2-(5-hydroxy-1H-indol-3-yl)acetic acid and carrying forward the (S,R) sulfinamide intermediate. MS (m/z) 535 $[M+H]^+$.

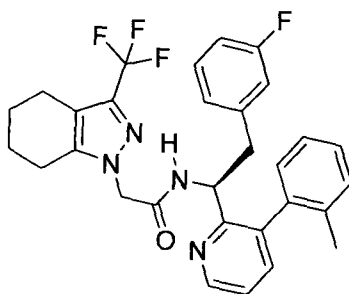
Example 24

**24**

The synthesis of (S)-N-(2-(3-fluorophenyl)-1-(3-o-tolylpyridin-2-yl)ethyl)-2-(5-hydroxy-1H-indol-3-yl)acetamide (**24**):

The title compound was prepared according to the method presented in the synthesis of Example 13 substituting o-tolylboronic acid for 4-methoxyphenylboronic acid and (3-fluorobenzyl)magnesium chloride for (3,5-difluorobenzyl)magnesium chloride. MS (m/z) 480 $[M+H]^+$.

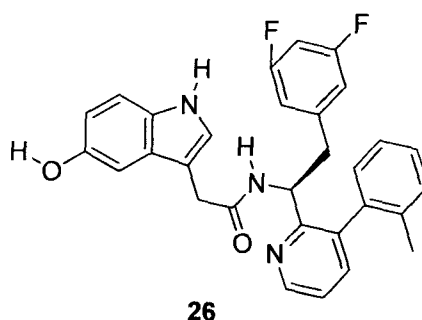
Example 25

**25**

The synthesis of (S)-N-(2-(3-fluorophenyl)-1-(3-o-tolylpyridin-2-yl)ethyl)-2-(3-(trifluoromethyl)-4,5,6,7-tetrahydro-1H-indazol-1-yl)acetamide (**25**):

The title compound was prepared according to the method presented in the synthesis of Example 13 substituting o-tolylboronic acid for 4-methoxyphenylboronic acid, (3-fluorobenzyl)magnesium chloride for (3,5-difluorobenzyl)magnesium chloride, and 2-(3-(trifluoromethyl)-4,5,6,7-tetrahydro-1H-indazol-1-yl)acetic acid for 2-(5-hydroxy-1H-indol-3-yl)acetic acid. MS (m/z) 537 $[M+H]^+$.

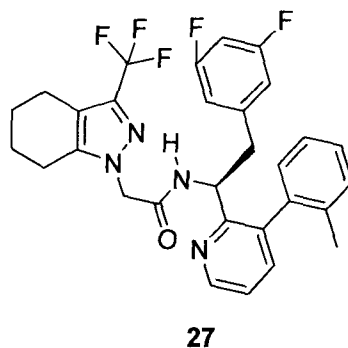
Example 26



The synthesis of (S)-N-(2-(3,5-difluorophenyl)-1-(3-o-tolylpyridin-2-yl)ethyl)-2-(5-hydroxy-1H-indol-3-yl)acetamide (**26**):

The title compound was prepared according to the method presented in the synthesis of Example 13 substituting o-tolylboronic acid for 4-methoxyphenylboronic acid. MS (m/z) 498 $[M+H]^+$.

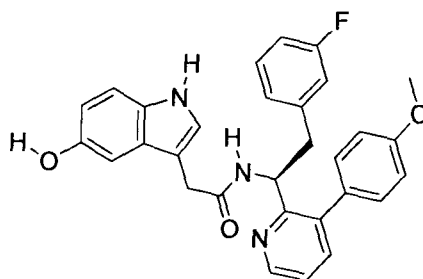
Example 27



The synthesis of (S)-N-(2-(3,5-difluorophenyl)-1-(3-o-tolylpyridin-2-yl)ethyl)-2-(3-(trifluoromethyl)-4,5,6,7-tetrahydro-1H-indazol-1-yl)acetamide (**27**):

The title compound was prepared according to the method presented in the synthesis of Example 13 substituting o-tolylboronic acid for 4-methoxyphenylboronic acid and 2-(3-(trifluoromethyl)-4,5,6,7-tetrahydro-1H-indazol-1-yl)acetic acid for 2-(5-hydroxy-1H-indol-3-yl)acetic acid. MS (m/z) 555 $[M+H]^+$.

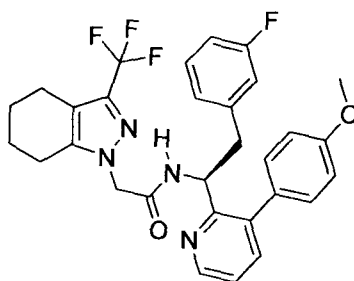
Example 28

**28**

The synthesis of (S)-N-(2-(3-fluorophenyl)-1-(3-(4-methoxyphenyl)pyridin-2-yl)ethyl)-2-(5-hydroxy-1H-indol-3-yl)acetamide (**28**):

The title compound was prepared according to the method presented in the synthesis of Example 13 substituting (3-fluorobenzyl)magnesium chloride for (3,5-difluorobenzyl)magnesium chloride. MS (m/z) 496 $[M+H]^+$.

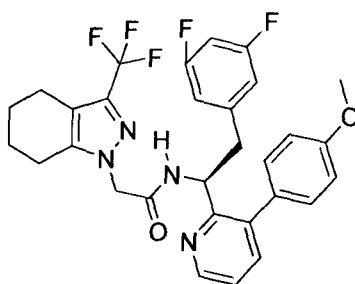
Example 29

**29**

The synthesis of (S)-N-(2-(3-fluorophenyl)-1-(3-(4-methoxyphenyl)pyridin-2-yl)ethyl)-2-(3-(trifluoromethyl)-4,5,6,7-tetrahydro-1H-indazol-1-yl)acetamide (**29**):

The title compound was prepared according to the method presented in the synthesis of Example 13 substituting (3-fluorobenzyl)magnesium chloride for (3,5-difluorobenzyl)magnesium chloride, and 2-(3-(trifluoromethyl)-4,5,6,7-tetrahydro-1H-indazol-1-yl)acetic acid for 2-(5-hydroxy-1H-indol-3-yl)acetic acid. MS (m/z) 553 $[M+H]^+$.

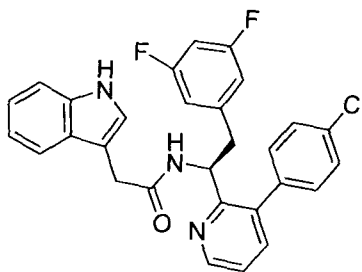
Example 30

**30**

The synthesis of (S)-N-(2-(3,5-difluorophenyl)-1-(3-(4-methoxyphenyl)pyridin-2-yl)ethyl)-2-(3-(trifluoromethyl)-4,5,6,7-tetrahydro-1H-indazol-1-yl)acetamide (**30**):

The title compound was prepared according to the method presented in the synthesis of Example 13 substituting 2-(3-(trifluoromethyl)-4,5,6,7-tetrahydro-1H-indazol-1-yl)acetic acid for 2-(5-hydroxy-1H-indol-3-yl)acetic acid. MS (m/z) 571 $[M+H]^+$.

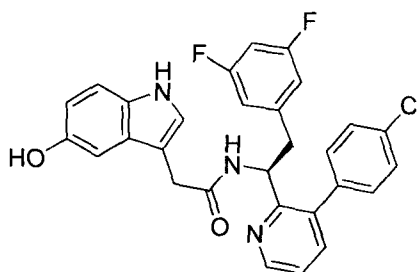
Example 31

**31**

The synthesis of (S)-N-(1-(3-(4-chlorophenyl)pyridin-2-yl)-2-(3,5-difluorophenyl)ethyl)-2-(1H-indol-3-yl)acetamide (**31**):

The title compound was prepared according to the method presented in the synthesis of Example 13 substituting 4-chlorophenylboronic acid for 4-methoxyphenylboronic acid and 2-(1H-indol-3-yl)acetic acid for 2-(5-hydroxy-1H-indol-3-yl)acetic acid. MS (m/z) 502 $[M+H]^+$.

Example 32

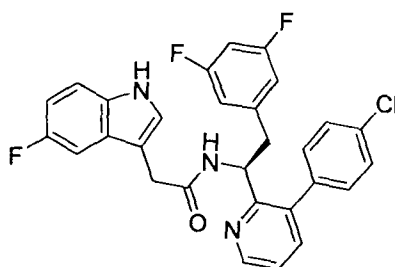
**32**

The synthesis of (S)-N-(1-(3-(4-chlorophenyl)pyridin-2-yl)-2-(3,5-difluorophenyl)ethyl)-2-(5-hydroxy-1H-indol-3-yl)acetamide (**32**):

The title compound was prepared according to the method presented for the synthesis of

- 5 Example 19 substituting 4-chlorophenylboronic acid for 4-methoxyphenylboronic acid. MS (m/z) 518 $[M+H]^+$.

Example 33

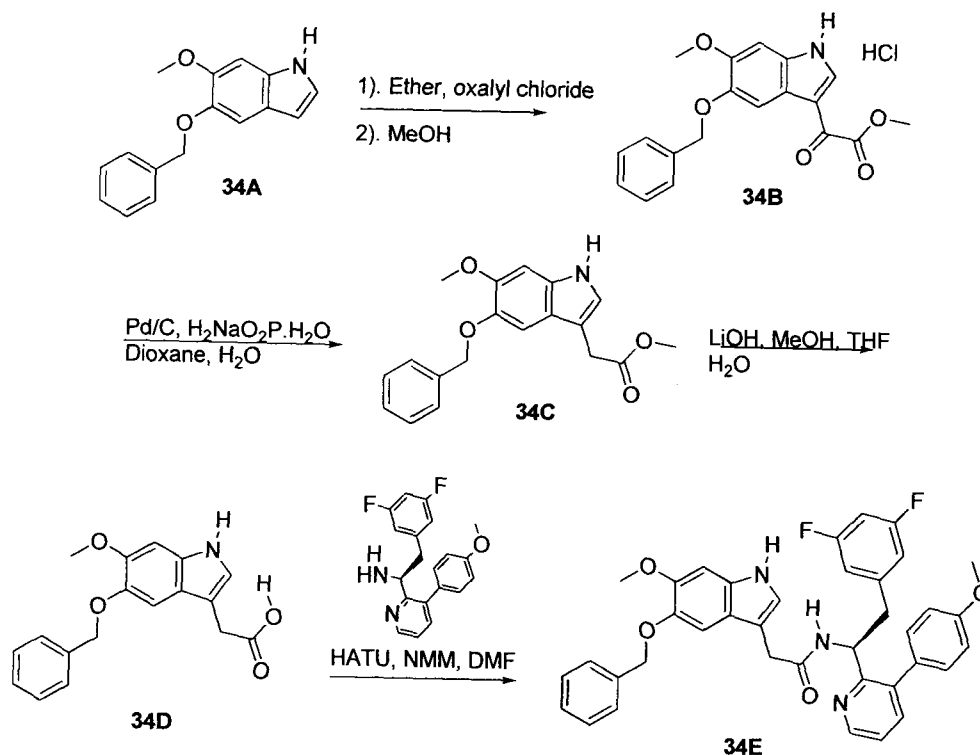
**33**

- 10 The synthesis of (S)-N-(1-(3-(4-chlorophenyl)pyridin-2-yl)-2-(3,5-difluorophenyl)ethyl)-2-(5-fluoro-1H-indol-3-yl)acetamide (**33**):

The title compound was prepared according to the method presented in the synthesis of Example 13 substituting 4-chlorophenylboronic acid for 4-methoxyphenylboronic acid and 2-(5-fluoro-1H-indol-3-yl)acetic acid for 2-(5-hydroxy-1H-indol-3-yl)acetic acid. MS (m/z) 502 $[M+H]^+$.

15

Example 34



Synthesis of methyl 2-(5-(benzyloxy)-6-methoxy-1H-indol-3-yl)-2-oxoacetate (**34B**):

A round bottom flask was charged with ether (3 ml) and 5-(benzyloxy)-6-methoxy-1H-indole (**34A**, 1g, 3.9 mmol) followed by slow addition of oxalyl chloride (0.34 ml, 3.9 mmol). The reaction was stirred for one minute after complete addition of all reagents then quickly filtered. The cake was soaked in 1 ml methanol after which the methanol was filtered off. This was repeated three times to give a 1200 mg of greenish/yellow colored solid which was used with no further purification. The yield was 82%. MS (m/z) 339.9 $[\text{M}+\text{H}]^+$.

Synthesis of methyl 2-(5-(benzyloxy)-6-methoxy-1H-indol-3-yl)acetate (**34C**):

A round bottom is charged with methyl 2-(5-(benzyloxy)-6-methoxy-1H-indol-3-yl)-2-oxoacetate (**34B**, 1200 mg, 3.2 mmol), dioxane (100 ml), Pd/C (300 mg), $\text{H}_2\text{NaO}_2\text{P}\cdot\text{H}_2\text{O}$ (3 mg, 28 mmol), and H_2O (40 ml). The resulting mixture was stirred at 95 °C until done as indicated by LC/MS. The reaction mixture was cooled to RT and filtered over a plug of celite, rinsing with ethyl acetate. The layers were partitioned and the organic layer was dried over sodium sulfate, filtered and concentrated to give a solid mixture of benzyl and de-benzylated solid which was used with no further purification. MS (m/z) 325.98 $[\text{M}+\text{H}]^+$.

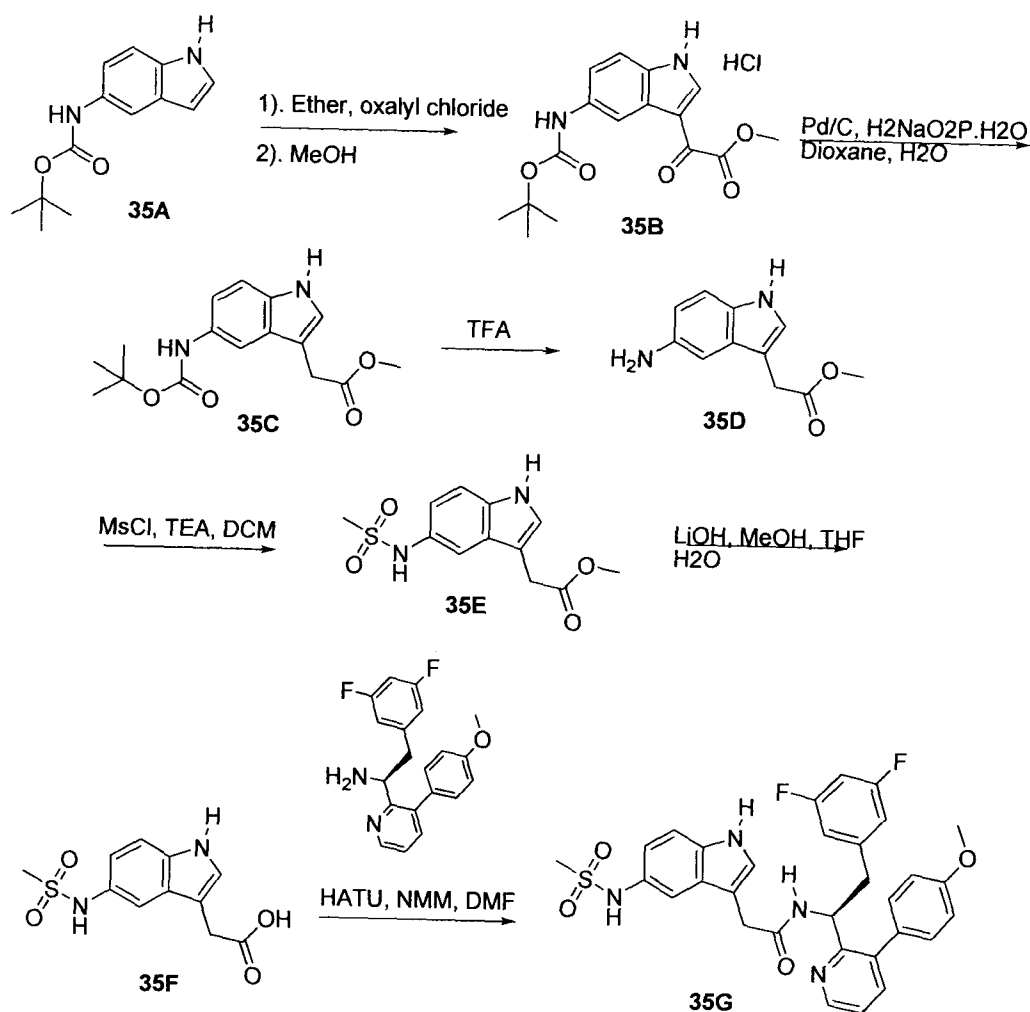
Synthesis of 2-(5-(benzyloxy)-6-methoxy-1H-indol-3-yl)acetic acid (**34D**):

A round bottom flask was charged with methyl 2-(5-(benzyloxy)-6-methoxy-1H-indol-3-yl)acetate (**34C**, 140 mg, mixture of benzyl and non benzyl), methanol (1 ml), and THF (1 ml). To the resulting mixture was added a solution of LiOH (60 mg, 2.5 mmol) dissolved in water (1 ml). The mixture was stirred until done after which the mixture was diluted with ethyl acetate and the layers separated, the aqueous layer was acidified and extracted 2X with ethyl acetate and the combined organic layers were dried over sodium sulfate, filtered and concentrated to give mixture of both benzyl and non-benzyl products as a solid which was used with no further purification. MS (m/z) 311.92 $[M+H]^+$

10 Synthesis of (S)-2-(5-(benzyloxy)-6-methoxy-1H-indol-3-yl)-N-(2-(3,5-difluorophenyl)-1-(3-(4-methoxyphenyl)pyridin-2-yl)ethyl)acetamide(**34E**):

A round bottom flask was charged with 2-(5-(benzyloxy)-6-methoxy-1H-indol-3-yl)acetic acid (66 mg, mixture of benzyl and non-benzyl), DMF (2 ml), N-methyl-morpholine (0.1 ml, 0.9 mmol), HATU (50 mg, 0.13 mmol), and (S)-2-(3,5-difluorophenyl)-1-(3-(4-methoxyphenyl)pyridin-2-yl)ethanamine (34 mg, 0.1 mmol). The mixture was stirred until done as indicated by LC/MS then filtered and purified by HPLC to afford the desired product (3.2 mg, 1H NMR ($(CD_3)_2SO$, 300 MHz) δ 10.50 (s, 1H), 8.53 (dd, 1H), 8.37 (d, 1H), 7.47 (dd, 1H), 7.41 (d, 2H), 7.35 (t, 2H), 7.30-7.27 (m, 2H), 7.11 (s, 1H), 7.07 (d, 2H), 6.88-6.85 (m, 5H), 6.33 (d, 2H), 5.25 (q, 1H), 4.89 (s, 2H), 3.74 (s, 3H), 3.39 (s, 2H), 2.88 (d, 2H), 2.78 (s, 3H); MS (m/z) 634.4 $[M+H]^+$.

Example 35



The synthesis of methyl 2-(5-(tert-butoxycarbonylamino)-1H-indol-3-yl)-2-oxoacetate hydrochloride (**35B**):

The title compound was prepared according to the method presented in the synthesis of methyl 2-(5-(benzyloxy)-6-methoxy-1H-indol-3-yl)-2-oxoacetate. Treatment of tert-butyl 1H-indol-5-ylcarbamate (10.8 mmol) occurred under the same conditions, adjusted for scale, to afford the desired compound. The yield was 76% as HCl salt. MS (*m/z*) 319.0 [M+H]⁺

The synthesis of methyl 2-(5-(tert-butoxycarbonylamino)-1H-indol-3-yl)acetate (**35C**):

The title compound was prepared according to the method presented in the synthesis of methyl 2-(5-(benzyloxy)-6-methoxy-1H-indol-3-yl)acetate. Treatment of methyl 2-(5-(tert-butoxycarbonylamino)-1H-indol-3-yl)-2-oxoacetate (7.0 mmol) occurred under the same conditions, adjusted for scale, to afford the desired product. The yield was 69%. MS (*m/z*) 249.15 [M+H-t-Butyl]⁺

Synthesis of methyl 2-(5-amino-1H-indol-3-yl)acetate (**35D**):

A round bottom flask was charged with methyl 2-(5-(tert-butoxycarbonylamino)-1H-indol-3-yl)acetate (1.35 g, 4.4 mmol) and TFA (4 ml). The mixture was stirred until done after which the mixture was concentrated to a light pink oil. The oil was diluted with DCM, sonicated, and
5 filtered to give 1660 mg of white solid which was used with no further purification. The yield was 76%. MS (*m/z*) 205.15 [M+H]⁺

Synthesis of methyl 2-(5-(methylsulfonamido)-1H-indol-3-yl)acetate (**35E**):

A round bottom flask was charged with methyl 2-(5-amino-1H-indol-3-yl)acetate (200 mg, 1
10 mmol), DCM (3 ml), and TEA (0.43 ml, 3.1 mmol) and cooled to 0 °C. To the resulting mixture MsCl (0.04 ml, 0.5 mmol) dissolved in DCM (2 ml) was added drop wise. The mixture was stirred until done after which the mixture was washed with a solution of 10% aqueous citric acid followed by a saturated solution of NaHCO₃. The organic layer was dried over sodium sulfate, concentrated by flash chromatography to give 80 mg of solid. The yield was 29%. MS (*m/z*)
15 282.9 [M+H]⁺.

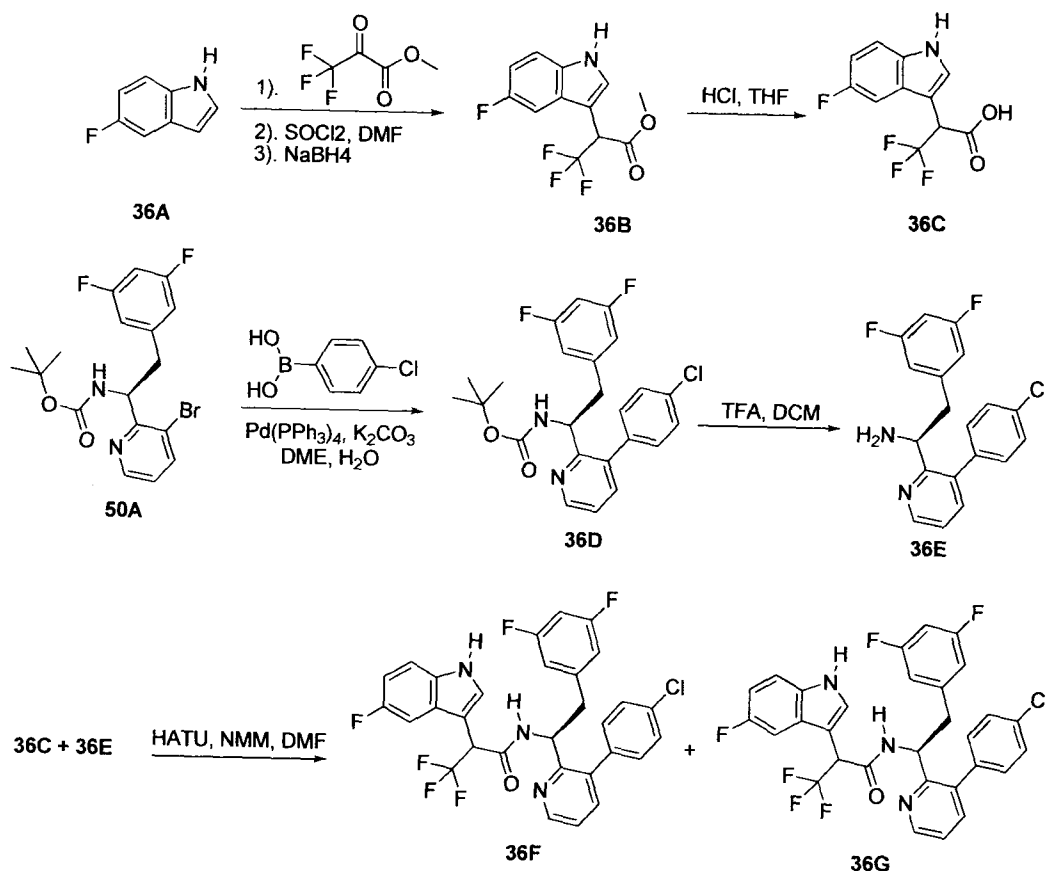
The synthesis of 2-(5-(methylsulfonamido)-1H-indol-3-yl)acetic acid (**35F**):

The title compound was prepared according to the method presented in the synthesis of 2-(5-(benzyloxy)-6-methoxy-1H-indol-3-yl)acetic acid. Treatment of methyl 2-(5-
20 (methylsulfonamido)-1H-indol-3-yl)acetate (0.28 mmol) occurred under the same conditions, adjusted for scale, to afford the desired product. The yield was 95%. MS (*m/z*) 268.8 [M+H]⁺.

The synthesis of (S)-N-(2-(3,5-difluorophenyl)-1-(3-(4-methoxyphenyl)pyridin-2-yl)ethyl)-2-(5-(methylsulfonamido)-1H-indol-3-yl)acetamide (**35G**):

25 The title compound was prepared according to the method presented in the synthesis of (S)-2-(5-(benzyloxy)-6-methoxy-1H-indol-3-yl)-N-(2-(3,5-difluorophenyl)-1-(3-(4-methoxyphenyl)pyridin-2-yl)ethyl)acetamide. Treatment of 2-(5-(methylsulfonamido)-1H-indol-3-yl)acetic acid (0.14 mmol) occurred under the same conditions, adjusted for scale, to afford the desired product. The mixture was stirred until done by LC/MS then filtered and purified by
30 HPLC to afford the desired product (3.7 mg, 4%): ¹H NMR ((CD₃)₂SO, 300 MHz) δ 10.84 (s, 1H), 9.15 (s, 1H), 8.58 (dd, 1H), 8.42 (d, 1H), 7.48 (dd, 1H), 7.36-7.35 (m, 1H), 7.32 (dd, 1H), 7.25 (d, 1H), 7.07 (s, 1H), 7.05 (d, 2H), 6.92 (dd, 1H), 6.87 (d, 3H), 6.32 (d, 2H), 5.24 (q, 1H), 3.74 (s, 3H), 3.47 (s, 2H), 2.89 (d, 2H), 2.78 (s, 3H); MS (*m/z*) 591.37 [M+H]⁺.

Examples 36



- 5 Synthesis of methyl 3,3,3-trifluoro-2-(5-fluoro-1H-indol-3-yl)-2-hydroxypropanoate (**36B**):
A round bottom flask was charged with 5-fluoro-1H-indole (3000 mg, 22.2 mmol) and methyl 3,3,3-trifluoro-2-oxopropanoate (2.27 ml, 22.2 mmol). The mixture was stirred until done and then diluted with DMF (100 ml), cool to 0°C and slowly add SOCl_2 (4 ml, 55.5 mmol) until peak has shifted by LC/MS. Slowly add NaBH_4 (2800 mg, 66.6 mmol) in portions and allow mixture to stir for 3 hours after which the mixture was dumped into stirring saturated NH_4Cl and resulting solids were filtered off and the mother liquor was extracted 2X ethyl acetate. The organic layer was dried over sodium sulfate and concentrated and purified by flash chromatography to yield 2.98 g of the desired compound in a yield of 49 %. MS (m/z) 275.9 $[\text{M}+\text{H}]^+$.

15 Synthesis of 3,3,3-trifluoro-2-(5-fluoro-1H-indol-3-yl)propanoic acid (**36C**):

A round bottom flask was charged with methyl 3,3,3-trifluoro-2-(5-fluoro-1H-indol-3-yl)-2-hydroxypropanoate (1000 mg, 3.6 mmol), HCl (4 ml), and THF (2 ml). The mixture was stirred

at 95°C for 3 days and then the cooled solution was extracted with ethyl acetate, the organic layer was extracted with saturated NaHCO₃, the aqueous layer was acidified and extract 2X with ethyl acetate and the combined organic layers were dried over sodium sulfate and concentrated to give 210 mg of solid which was used with no further purification. The yield was 22%. MS
5 (*m/z*) 262.1 [M+H]⁺.

Synthesis of (S)-tert-butyl 1-(3-(4-chlorophenyl)pyridin-2-yl)-2-(3,5-difluorophenyl)ethylcarbamate (**36D**):

A round bottom flask was charged with **50A** (1 g, 2.4 mmol), DME (40 ml), 4-
10 chlorophenylboronic acid (454 mg, 3 mmol), Pd(PPh₃)₄ (280 mg, 0.24 mmol) and K₂CO₃ (669 mg, 4.8 mmol) dissolved in water (5 ml). The mixture was heated overnight at 85 °C. Allow the reaction to cool then dilute with H₂O and extract 2X EtOAc. The combined organic layers were washed with brine then dried over sodium sulfate, concentrated, and purified by flash chromatography to give 692 mg of desired compound. The yield was 64%. MS (*m/z*) 445.3
15 [M+H]⁺.

Synthesis of (S)-1-(3-(4-chlorophenyl)pyridin-2-yl)-2-(3,5-difluorophenyl)ethanamine trifluoroacetate (**36E**):

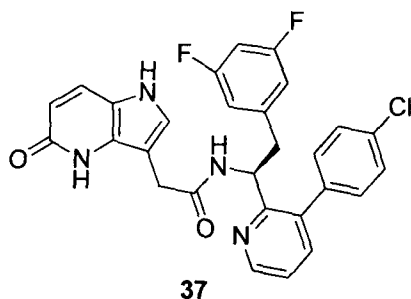
A round bottom flask was charged with (S)-tert-butyl 1-(3-(4-chlorophenyl)pyridin-2-yl)-2-(3,5-
20 difluorophenyl)ethylcarbamate (690 mg, 1.6 mmol) and TFA:DCM 1:2.5 (7 ml). The reaction was stirred at room temperature until done by LC/MS then concentrated 2X from DCM. The crude solid was used as is in next reaction. MS (*m/z*) 345.3 [M+H]⁺.

Synthesis of compounds N-((S)-1-(3-(4-chlorophenyl)pyridin-2-yl)-2-(3,5-

25 difluorophenyl)ethyl)-3,3,3-trifluoro-2-(5-fluoro-1H-indol-3-yl)propanamide (**36F** and **36G**):
A 2 dram vial was charged with **36C** (200 mg, 0.8 mmol), **36E** (240 mg, 0.7 mmol), HATU (351 mg, 0.9 mmol), NMM (0.1 ml, 0.6 mmol) and DMF (6 ml). The mixture was stirred until done by LC/MS then diluted with a 1:1 mixture of TFA:water (0.5 ml), filtered and purified by HPLC to afford the separated diastereomeric products (**36F**, 52.9 mg, 12%; **36G**, 166.1 mg, 37%): **36F**
30 ¹H NMR ((CD₃)₂SO, 300 MHz) δ 11.27 (s, 1H), 8.98 (dd, 1H), 8.67 (dd, 1H), 7.59 (dd, 1H), 7.47 (d, 2H), 7.41 (dd, 1H), 7.35-7.31 (m, 3H), 7.21 (d, 2H), 6.90 (dt, 1H), 6.69 (dt, 1H), 6.21 (d, 2H), 5.17 (q, 1H), 4.95 (q, 1H), 2.83 (m, 2H); MS (*m/z*) 588.6 [M+H]⁺. **36G** ¹H NMR ((CD₃)₂SO, 300 MHz) δ 11.27 (s, 1H), 8.98 (dd, 1H), 8.51 (dd, 1H), 7.50 (dd, 1H), 7.38-7.28

(m, 6H), 7.05 (d, 2H), 6.96 (dt, 1H), 6.90 (dt, 1H), 6.50 (d, 2H), 5.15 (q, 1H), 4.90 (q, 1H), 3.00-2.98 (m, 2H); MS (m/z) 588.6 $[M+H]^+$.

Example 37



5

The synthesis of (S)-N-(1-(3-(4-chlorophenyl)pyridin-2-yl)-2-(3,5-difluorophenyl)ethyl)-2-(5-oxo-4,5-dihydro-1H-pyrrolo[3,2-b]pyridin-3-yl)acetamide (**37**):

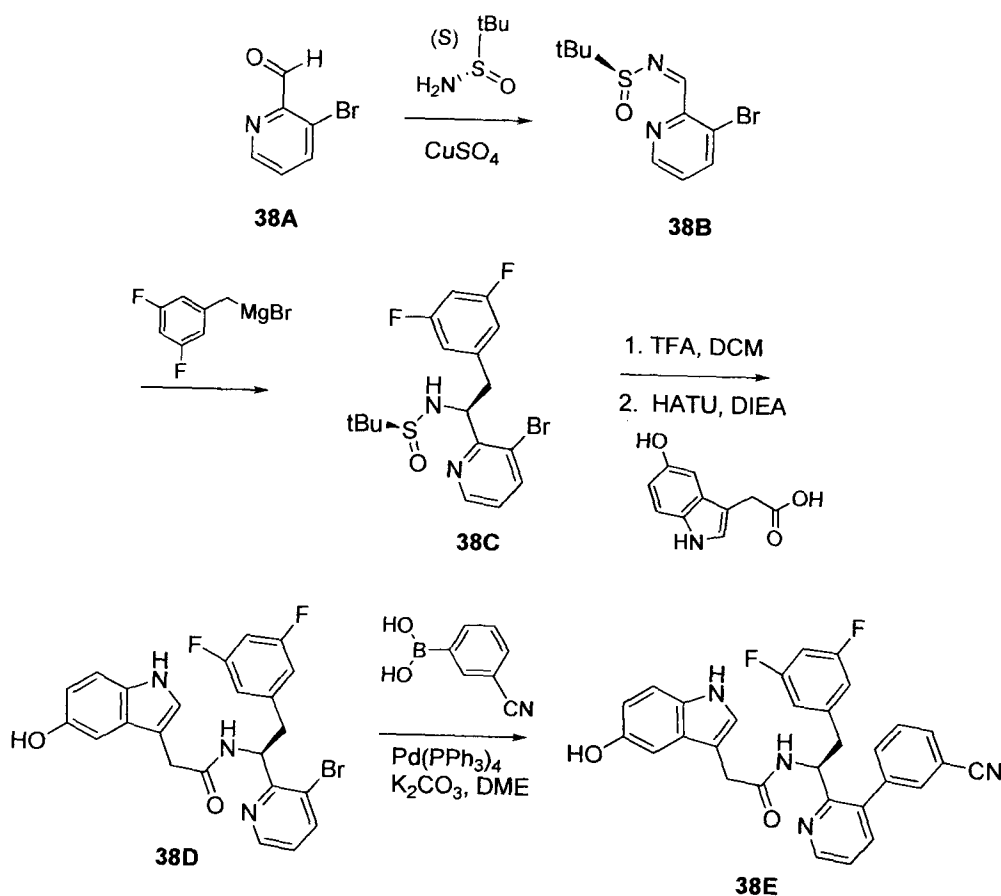
The title compound was prepared according to the method presented in the synthesis of Example 13 substituting 4-chlorophenylboronic acid for 4-methoxyphenylboronic acid and 2-(5-oxo-4,5-

10

dihydro-1H-pyrrolo[3,2-b]pyridin-3-yl)acetic acid for 2-(5-hydroxy-1H-indol-3-yl)acetic acid.

MS (m/z) 519 $[M+H]^+$.

Example 38



Synthesis of (S)-N-((3-bromopyridin-2-yl)methylene)-2-methylpropane-2-sulfonamide (**38B**):

The title compound was prepared according to the procedure described in the synthesis of **13C** in Example 13 utilizing 3-bromopicolinaldehyde. MS (m/z) 288.9 $[\text{M}+\text{H}]^+$.

5

Synthesis of (S)-N-((S)-1-(3-bromopyridin-2-yl)-2-(3,5-difluorophenyl)ethyl)-2-methylpropane-2-sulfonamide (**38C**):

The title compound was prepared according to the procedure described in the synthesis of **13E** in Example 13 utilizing **38B**. MS (m/z) 417.1 $[\text{M}+\text{H}]^+$.

10

Synthesis of (S)-N-((S)-1-(3-bromopyridin-2-yl)-2-(3,5-difluorophenyl)ethyl)-2-(5-hydroxy-1H-indol-3-yl)acetamide (**38D**):

A solution of (S)-N-((S)-1-(3-bromopyridin-2-yl)-2-(3,5-difluorophenyl)ethyl)-2-

methylpropane-2-sulfonamide (1 g, 2.4 mmol) in 6 ml of HCl (2N/ 4 ml of MeOH and 2 ml of 1,4-dioxane) was stirred for 3 hours. The solvent was removed and the crude product was dried by high vacuum. Used without further purification. To a solution of 2-(5-hydroxy-1H-indol-3-yl)acetic acid (304 mg, 1.58 mmol) and DIEA (0.6 ml, 3.32 mmol) in DMF (5 ml), was added HATU (630 mg, 1.66 mmol). After 20 minutes, the crude product from last step in 5 ml of DMF

15

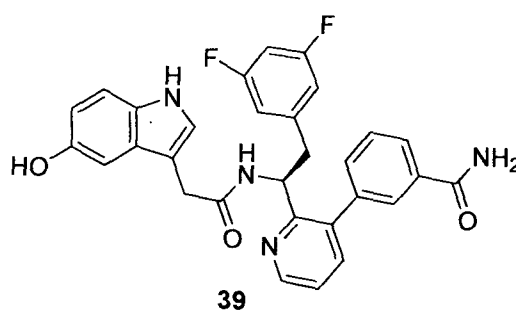
was added to the solution. It was stirred for 2 hours. The DMF solution was removed.

Redissolved in 100 ml of EtOAc and washed with NaHCO₃ (aq) and brine. The organic layer was dried over Na₂SO₄, filtered and concentrated. Purified the crude product by flash column (Rf: 0.3 MeOH/DCM = 5%). The yield was (486mg, 1.15 mmol). 48 % for two steps. ¹H NMR (*d*-CD₃OD, 400 MHz) δ 8.36 (d, 1H), 7.9 (d, 1H), 7.11-7.17 (m, 2H), 7.035 (s, 1H), 6.8 (s, 1H), 6.6-6.7 (m, 2H), 6.51-6.53 (m, 2H), 5.73 (t, 1H), 3.57 (s, 2H), 3.0-3.1 (m, 1H), 2.9-3.9 (m, 1H); MS (*m/z*) 486 [M+H]⁺.

Synthesis of (S)-N-(1-(3-(3-cyanophenyl)pyridin-2-yl)-2-(3,5-difluorophenyl)ethyl)-2-(5-hydroxy-1H-indol-3-yl)acetamide (**38E**):

A mixture of (S)-N-(1-(3-bromopyridin-2-yl)-2-(3,5-difluorophenyl)ethyl)-2-(5-hydroxy-1H-indol-3-yl)acetamide (48.7mg, 0.1 mmol), potassium carbonate (27 mg, 0.2 mmol) in 0.5 ml of water, tetrakis(triphenylphosphine)palladium(0) (8 mg, 0.007 mmol) and 3-cyanophenylboronic acid (0.12 mmol) in DME (1.5 mL) was heated at 120 °C for 30 minutes under microwave irradiation. Solvents were concentrated *in vacuo* and the residue was purified by RP HPLC using a C18 column to provide the title product: ¹H NMR (*d*-DMSO, 400 MHz) δ 10.46 (s, 1H), 8.68 (d, 1H), 8.53 (d, 1H), 7.81 (d, 1H), 7.51-7.55 (m, 4H), 7.46 (s, 1H), 7.36-7.38 (m, 1H), 7.05 (s, 1H), 6.89-6.94 (m, 2H), 6.8 (s, 1H), 6.53 (d, 1H), 6.34 (d, 1H), 5.09 (q, 1H), 3.41 (q, 2H), 2.8-3.0 (m, 2H); MS (*m/z*) 509 [M+H]⁺.

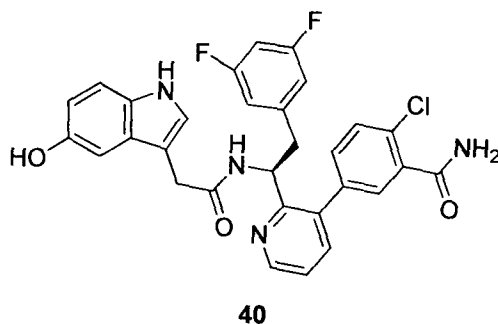
Example 39



The synthesis of (S)-3-(2-(2-(3,5-difluorophenyl)-1-(2-(5-hydroxy-1H-indol-3-yl)acetamido)ethyl)pyridin-3-yl)benzamide (**39**):

The title compound was prepared according to the method presented in the synthesis of Example 38 substituting 3-carbamoylphenylboronic acid for 3-cyanophenylboronic acid. MS (*m/z*) 527 [M+H]⁺.

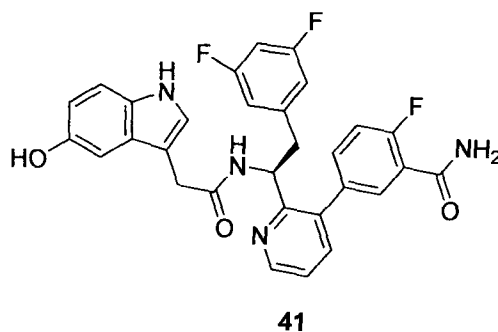
Example 40



5 The synthesis of (S)-2-chloro-5-(2-(2-(3,5-difluorophenyl)-1-(2-(5-hydroxy-1H-indol-3-yl)acetamido)ethyl)pyridin-3-yl)benzamide (**40**):

The title compound was prepared according to the method presented in the synthesis of Example 38 substituting 3-carbamoyl-4-chlorophenylboronic acid for 3-cyanophenylboronic acid. MS (m/z) 561 $[M+H]^+$.

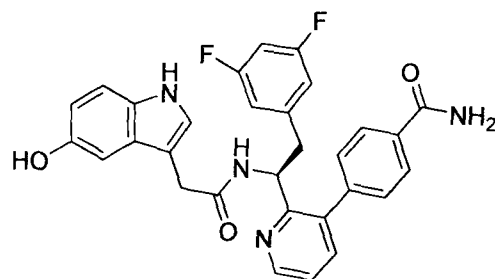
10 Example 41



The synthesis of (S)-5-(2-(2-(3,5-difluorophenyl)-1-(2-(5-hydroxy-1H-indol-3-yl)acetamido)ethyl)pyridin-3-yl)-2-fluorobenzamide (**41**):

15 The title compound was prepared according to the method presented in the synthesis of Example 38 substituting 3-carbamoyl-4-fluorophenylboronic acid for 3-cyanophenylboronic acid. MS (m/z) 545 $[M+H]^+$.

Example 42

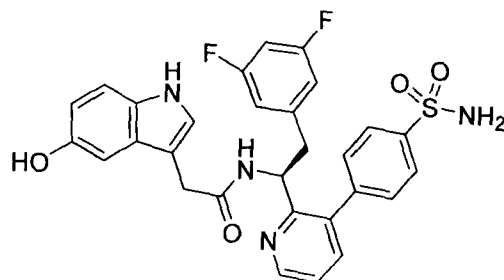


42

The synthesis of (S)-4-(2-(2-(3,5-difluorophenyl)-1-(2-(5-hydroxy-1H-indol-3-yl)acetamido)ethyl)pyridin-3-yl)benzamide (**42**):

The title compound was prepared according to the method presented in the synthesis of Example 38 substituting 4-carbamoylphenylboronic acid for 3-cyanophenylboronic acid. MS (m/z) 527 $[M+H]^+$.

Example 43

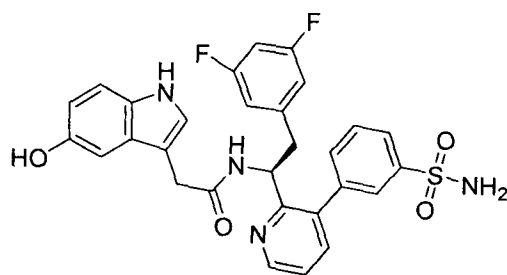


43

The synthesis of (S)-N-(2-(3,5-difluorophenyl)-1-(3-(4-sulfamoylphenyl)pyridin-2-yl)ethyl)-2-(5-hydroxy-1H-indol-3-yl)acetamide (**43**):

The title compound was prepared according to the method presented in the synthesis of Example 38 substituting 4-sulfamoylphenylboronic acid for 3-cyanophenylboronic acid. MS (m/z) 563 $[M+H]^+$.

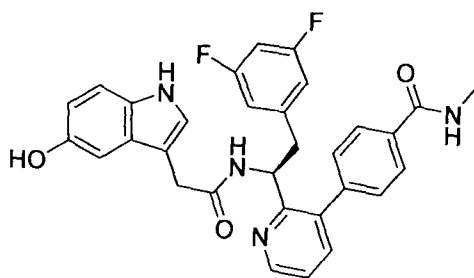
Example 44

**44**

The synthesis of (S)-N-(2-(3,5-difluorophenyl)-1-(3-(3-sulfamoylphenyl)pyridin-2-yl)ethyl)-2-(5-hydroxy-1H-indol-3-yl)acetamide (**44**):

The title compound was prepared according to the method presented in the synthesis of Example 38 substituting 3-sulfamoylphenylboronic acid for 3-cyanophenylboronic acid. MS (m/z) 563 $[M+H]^+$.

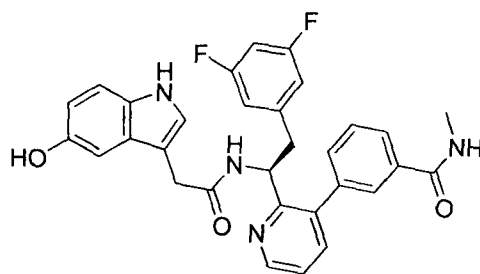
Example 45

**45**

The synthesis of (S)-4-(2-(2-(3,5-difluorophenyl)-1-(2-(5-hydroxy-1H-indol-3-yl)acetamido)ethyl)pyridin-3-yl)-N-methylbenzamide (**45**):

The title compound was prepared according to the method presented in the synthesis of Example 38 substituting 4-(methylcarbamoyl)phenylboronic acid for 3-cyanophenylboronic acid. MS (m/z) 540 $[M+H]^+$.

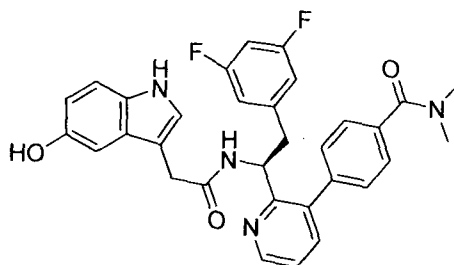
Example 46

**46**

The synthesis of (S)-3-(2-(2-(3,5-difluorophenyl)-1-(2-(5-hydroxy-1H-indol-3-yl)acetamido)ethyl)pyridin-3-yl)-N-methylbenzamide (**46**):

The title compound was prepared according to the method presented in the synthesis of Example 38 substituting 3-(methylcarbamoyl)phenylboronic acid for 3-cyanophenylboronic acid. MS (m/z) 540 $[M+H]^+$.

Example 47

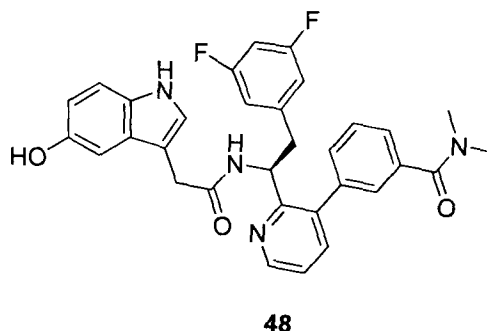
**47**

10 The synthesis of (S)-4-(2-(2-(3,5-difluorophenyl)-1-(2-(5-hydroxy-1H-indol-3-yl)acetamido)ethyl)pyridin-3-yl)-N,N-dimethylbenzamide (**47**):

The title compound was prepared according to the method presented in the synthesis of Example 38 substituting 4-(dimethylcarbamoyl)phenylboronic acid for 3-cyanophenylboronic acid. MS (m/z) 555 $[M+H]^+$.

15

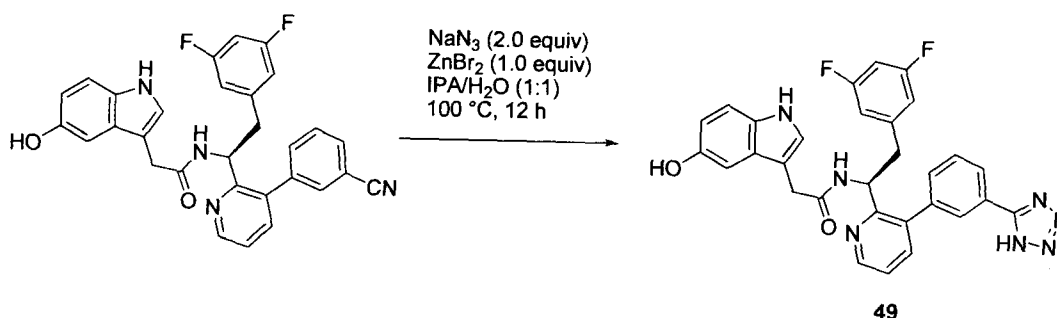
Example 48



The synthesis of (S)-3-(2-(2-(3,5-difluorophenyl)-1-(2-(5-hydroxy-1H-indol-3-yl)acetamido)ethyl)pyridin-3-yl)-N,N-dimethylbenzamide (**48**):

The title compound was prepared according to the method presented in the synthesis of Example 38 substituting 3-(dimethylcarbamoyl)phenylboronic acid for 3-cyanophenylboronic acid. MS (m/z) 555 $[M+H]^+$.

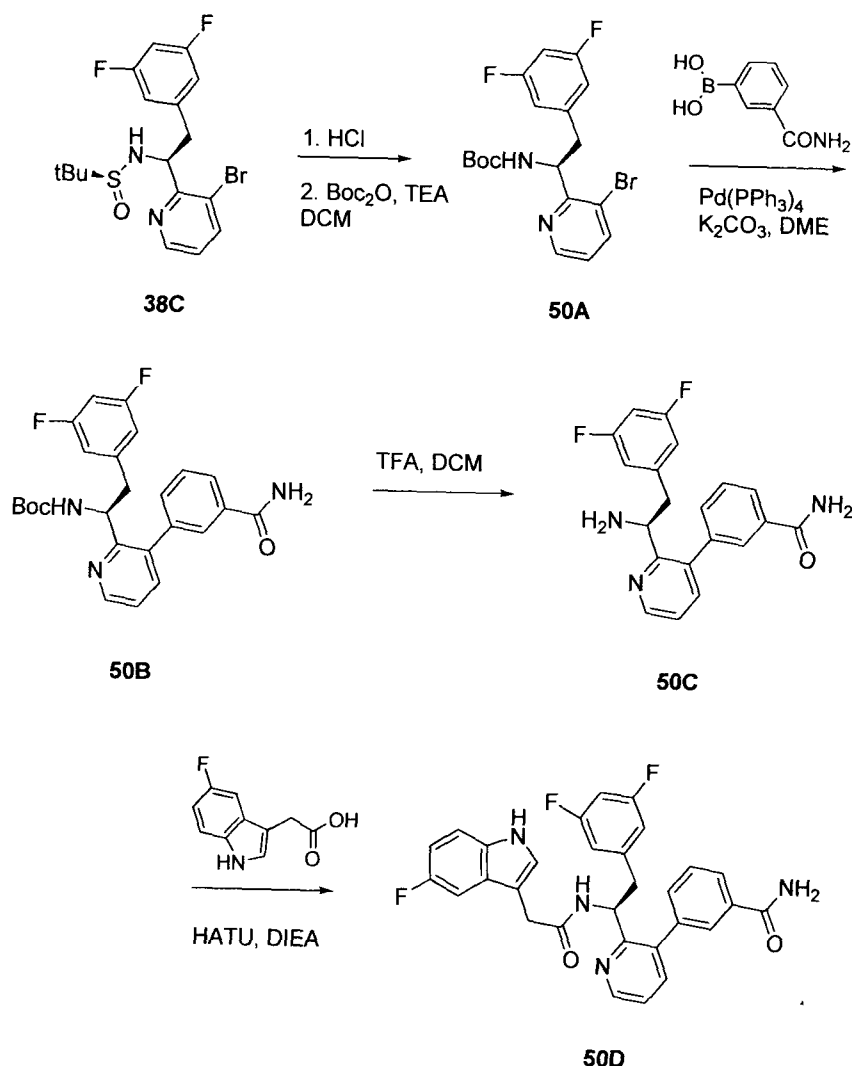
Example 49



The synthesis of (S)-N-(1-(3-(3-(1H-tetrazol-5-yl)phenyl)pyridin-2-yl)-2-(3,5-difluorophenyl)ethyl)-2-(5-hydroxy-1H-indol-3-yl)acetamide (**49**):

To a solution of (S)-N-(1-(3-(3-cyanophenyl)pyridin-2-yl)-2-(3,5-difluorophenyl)ethyl)-2-(5-hydroxy-1H-indol-3-yl)acetamide (10 mg, 0.02 mmol) in a mixture of 1 mL isopropanol and 1 mL water in a 5 mL microwave tube was added $ZnBr_2$ (4.5 mg, 0.02 mmol) and NaN_3 (2.6 mg, 0.04 mmol) at room temperature. The tube was sealed and the mixture was heated at 100 °C overnight. After the completion of the reaction, the mixture was purified by reverse phase HPLC to afford the desired product (3.4 mg, 0.006 mmol); MS (m/z): 552.1 $[M+H]^+$.

Example 50



Synthesis of (S)-tert-butyl 1-(3-bromopyridin-2-yl)-2-(3,5-difluorophenyl)ethylcarbamate (50A):

Mixed 1.5M HCl/MeOH (2ml) and 4N HCl/1,4-dioxane (1.0 ml) together. Added the resulting solution to the N-((S)-1-(3-bromopyridin-2-yl)-2-(3,5-difluorophenyl)ethyl)-2-methylpropane-2-sulfonamide (1.02g, 2.44 mmol). After 10 min, concentrated reaction mixture in vacuo. Co-evaporated residue with Et₂O until material became a solid. Collected solid by filtration. Suspended solids (702 mg, 2.01 mmol) in CH₂Cl₂. Di-tert-butyl dicarbonate (482mg, 2.21mmol) was added to the suspension followed by triethylamine (560 μl, 4.02mmol). Stirred reaction at room temperature for 30 min. Concentrated reaction in vacuo. Partitioned residue between EtOAc and H₂O. Extracted aqueous layer 2x with EtOAc. Washed combined organics with brine. Dried organics over MgSO₄, filtered and concentrated. Purified residue on 40g SiO₂ column using EtOAc/hex (rf = 0.47 in 20%EtOAc/hex.). Combined pure fractions and concentrated. Dried solid on high vacuum for 3hrs. The yield was 736mg.

Synthesis of (S)-tert-butyl 1-(3-(3-carbamoylphenyl)pyridin-2-yl)-2-(3,5-difluorophenyl)ethylcarbamate (**50B**):

Dissolved (S)-tert-butyl 1-(3-bromopyridin-2-yl)-2-(3,5-difluorophenyl)ethylcarbamate (736 mg, 1.78 mmol) and 3-carbamoylphenylboronic (352mg, 2.14mmol) in 1,2-dimethoxyethane.

- 5 Added 0.4N aq. K_2CO_3 (515 μ l, 3.56 mmol) and degassed reaction by evacuation and purge with N_2 (3x). Added $Pd(PPh_3)_4$ (206 mg, 0.178 mmol) and degassed again. Heated reaction at 80 °C overnight. LC/MS of reaction mixture shows complete conversion to product. Filtered cooled reaction mixture through celite, washing with EtOAc. Partitioned filtrate between EtOAc and H_2O . Extracted aqueous layer 2x with EtOAc. Washed combined organics with brine. Dried
- 10 organics over $MgSO_4$, filtered and concentrated. Purified residue on 40g SiO_2 column using EtOAc/hex (rf = 0.25 in 50%EtOAc/hex.) Combined pure fractions and concentrated. Dried solid on high vacuum for 3hrs. The yield was 750mg. 1H NMR (400 MHz, $CDCl_3$) δ 8.64 (dd, J = 4.7, 1.5 Hz, 1H), 7.96 (d, J = 7.7 Hz, 1H), 7.72 (s, 2H), 7.43 (dd, J = 16.4, 8.6 Hz, 2H), 7.24 (s, 1H), 6.83 (d, J = 7.4 Hz, 1H), 6.50 (t, J = 9.0 Hz, 1H), 6.06 (d, J = 6.2 Hz, 2H), 5.79 (s, 1H),
- 15 5.67 (s, 1H), 5.39 (m, 1H), 2.93 (m, 2H), 1.42 (s, 9H).

Synthesis of (S)-3-(2-(1-amino-2-(3,5-difluorophenyl)ethyl)pyridin-3-yl)benzamide trifluoroacetate (**50C**):

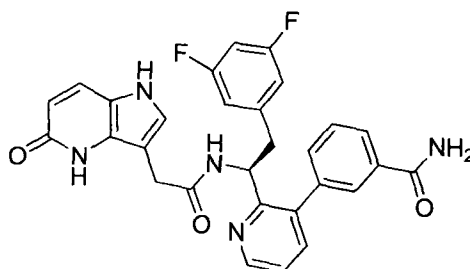
- (S)-tert-butyl 1-(3-(3-carbamoylphenyl)pyridin-2-yl)-2-(3,5-difluorophenyl)ethylcarbamate (750mg, 1.65mmol) was dissolved in 5ml CH_2Cl_2 . To the solution was added 5ml of trifluoroacetic acid. The reaction was stirred at room temperature for 30min. Concentrated reaction mixture in vacuo. Dried resulting solid on high vacuum overnight. The yield was 759mg.
- 20

- 25 Synthesis of (S)-3-(2-(2-(3,5-difluorophenyl)-1-(2-(5-fluoro-1H-indol-3-yl)acetamido)ethyl)pyridin-3-yl)benzamide (**50D**):

- Combined (S)-3-(2-(1-amino-2-(3,5-difluorophenyl)ethyl)pyridin-3-yl)benzamide trifluoroacetate (133 mg, 0.285 mmol) 2-(5-fluoro-1H-indol-3-yl)acetic acid (50 mg, 0.259 mmol), and HATU (108 mg, 0.285 mmol) in 20ml vial. Added DMF and stirred to dissolve the
- 30 solids. Added diisopropylethylamine (135 μ l, 0.77 mmol) and stirred reaction at room temperature for 90min. Purified reaction mixture on prep reverse phase HPLC using 20-80%B (A=0.1%TFA/ H_2O ;B=0.1%TFA/ACN). Combined pure fractions as determined by LC/MS and lyophilized. The yield was 98mg. 1H NMR (400 MHz, d -DMSO) δ 10.89 (s,1H), 8.66(m,2H),

7.95 (s,1H), 7.86 (d,1H), 7.73 (s,1H), 7.62 (dd,1H), 7.44 (m,4H), 7.22 (dd,1H), 7.10 (m,2H), 6.84 (m,2H), 6.47(d,2H), 5.73(broad), 5.19 (m,1H), 3.44 (d,2H), 2.94 (m, 2H); MS (m/z) 529 $[M+H]^+$.

5 Example 51

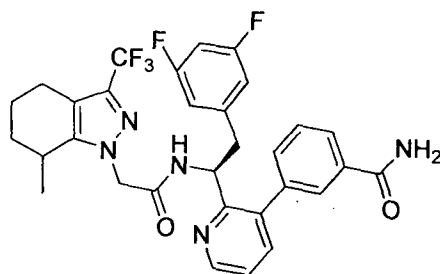


51

The synthesis of (S)-3-(2-(2-(3,5-difluorophenyl)-1-(2-(5-oxo-4,5-dihydro-1H-pyrrolo[3,2-b]pyridin-3-yl)acetamido)ethyl)pyridin-3-yl)benzamide (**51**):

The title compound was prepared according to the method presented for the synthesis of Example 50 substituting 2-(5-oxo-4,5-dihydro-1H-pyrrolo[3,2-b]pyridin-3-yl)acetic acid for 2-(5-fluoro-1H-indol-3-yl)acetic acid. MS (m/z) 528 $[M+H]^+$.

Example 52

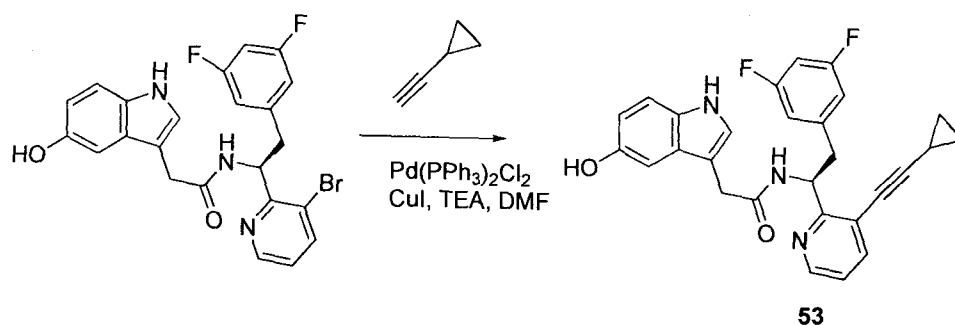


52

The synthesis of 3-(2-((1S)-2-(3,5-difluorophenyl)-1-(2-(7-methyl-3-(trifluoromethyl)-4,5,6,7-tetrahydro-1H-indazol-1-yl)acetamido)ethyl)pyridin-3-yl)benzamide (**52**):

The title compound was prepared according to the method presented for the synthesis of Example 50 substituting 2-(7-methyl-3-(trifluoromethyl)-4,5,6,7-tetrahydro-1H-indazol-1-yl)acetic acid for 2-(5-fluoro-1H-indol-3-yl)acetic acid. MS (m/z) 598 $[M+H]^+$.

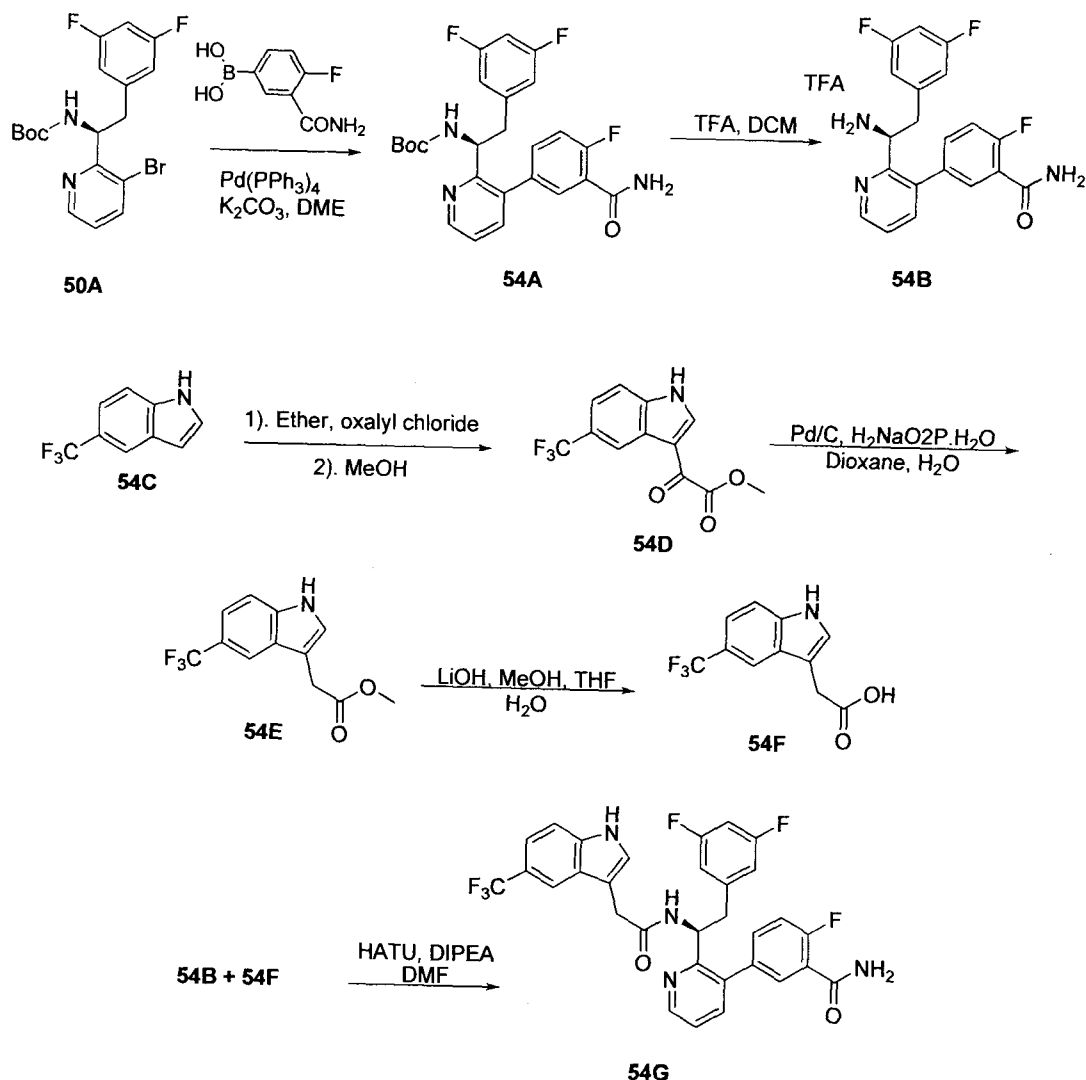
Example 53



Synthesis of (S)-N-(1-(3-(cyclopropylethynyl)pyridin-2-yl)-2-(3,5-difluorophenyl)ethyl)-2-(5-hydroxy-1H-indol-3-yl)acetamide (**53**):

To a solution of (S)-N-(1-(3-bromopyridin-2-yl)-2-(3,5-difluorophenyl)ethyl)-2-(5-hydroxy-1H-indol-3-yl)acetamide (97.4 mg, 0.2 mmol), bis(triphenylphosphine)dichloro palladium (15 mg, 0.021 mmol), copper(I) iodide (4 mg, 0.021 mmol) in DMF (0.36 ml) and triethylamine (0.6 ml), ethynylcyclopropane (20.8 mg, 0.315 mmol) was added to the solution. It was heated at 120°C for 120 minutes under microwave irradiation. Solvents were concentrated *in vacuo* and the residue was purified by RP HPLC using a C18 column with a gradient of H₂O, 0.1% TFA-acetonitrile, to provide the desired product. ¹H NMR (*d*-DMSO, 400 MHz) δ 10.46 (s, 1H), 8.48 (d, 1H), 8.25 (d, 1H), 7.66 (d, 1H), 7.2-7.3 (m, 1H), 7.1-7.2 (d, 1H), 6.9-7.0 (m, 2H), 6.78 (s, 1H), 6.65-6.75 (m, 2H), 6.53 (d, 1H), 5.56 (q, 1H), 3.41 (q, 2H), 2.8-3.0 (m, 2H), 1.5-1.6 (m, 1H), 1.8-1.9 (m, 2H), 1.6-1.7 (m, 2H); MS (*m/z*) 472 [M+H]⁺

Example 54



Synthesis of (S)-tert-butyl 1-(3-(3-carbamoyl-4-fluorophenyl)pyridin-2-yl)-2-(3,5-difluorophenyl)ethylcarbamate (**54A**):

A round bottom flask was charged with **50A** (3 g, 7.3 mmol), DME (100 ml), 3-carbamoyl-4-fluorophenylboronic acid (1.6 g, 8.7 mmol), $\text{Pd(PPh}_3)_4$ (419 mg, 0.36 mmol) and K_2CO_3 (2 g, 14.5 mmol) dissolved in water (12 ml). Heat the stirring mixture overnight at 85 °C. Allow the reaction to cool then dilute with H_2O and extract 2X EtOAc. The combined organic layers were washed with brine then dried over sodium sulfate, concentrated, and purified by flash chromatography to give the title compound (1.8 g, 53%): MS (m/z) 472.6 [$\text{M}+\text{H}$] $^+$.

Synthesis of (S)-5-(2-(1-amino-2-(3,5-difluorophenyl)ethyl)pyridin-3-yl)-2-fluorobenzamide trifluoroacetate (**54B**):

A round bottom flask was charged with (S)-tert-butyl 1-(3-(3-carbamoyl-4-fluorophenyl)pyridin-2-yl)-2-(3,5-difluorophenyl)ethylcarbamate (1 g, 2.2 mmol) and TFA:DCM 1:1 (4 ml). The reaction was stirred at room temperature until complete

disappearance of starting materials then concentrated 2X from DCM. The crude solid was used as is in next reaction: MS (m/z) 372.4 $[M+H]^+$.

Synthesis of methyl 2-oxo-2-(5-(trifluoromethyl)-1H-indol-3-yl)acetate (**54D**):

- 5 A round bottom flask was charged with ether (2 ml) and 5-(trifluoromethyl)-1H-indole (3g, 16.2 mmol) followed by slow addition of oxalyl chloride (3 ml, 34 mmol). The reaction was stirred for 15 minutes after complete addition of all reagents then filtered. The cake was rinsed with ether then soaked in 6 ml methanol after which the methanol was filtered off (repeated 3 times). Drying under vacuum gave 3 g of the desired compound as the HCl salt which was used with no
10 further purification. The yield was 60%. MS (m/z) 272.1 $[M+H]^+$.

Synthesis of methyl 2-(5-(trifluoromethyl)-1H-indol-3-yl)acetate (**54E**):

- A round bottom is charged with methyl 2-oxo-2-(5-(trifluoromethyl)-1H-indol-3-yl)acetate (3 g, 9.8 mmol), dioxane (200 ml), Pd/C (1 g), $H_2NaO_2P \cdot H_2O$ (6 g, 57 mmol), and H_2O (18 ml). The
15 resulting mixture was stirred at 125 °C until complete disappearance of starting material. The reaction mixture was cooled to RT and filtered over a plug of celite, rinsing with ethyl acetate. The layers were partitioned and the organic layer was dried over sodium sulfate, filtered, concentrated and purified by flash chromatography to give the desired compound (1.3 g, 50%):
MS (m/z) 258.1 $[M+H]^+$.

20

Synthesis of 2-(5-(trifluoromethyl)-1H-indol-3-yl)acetic acid (**54F**):

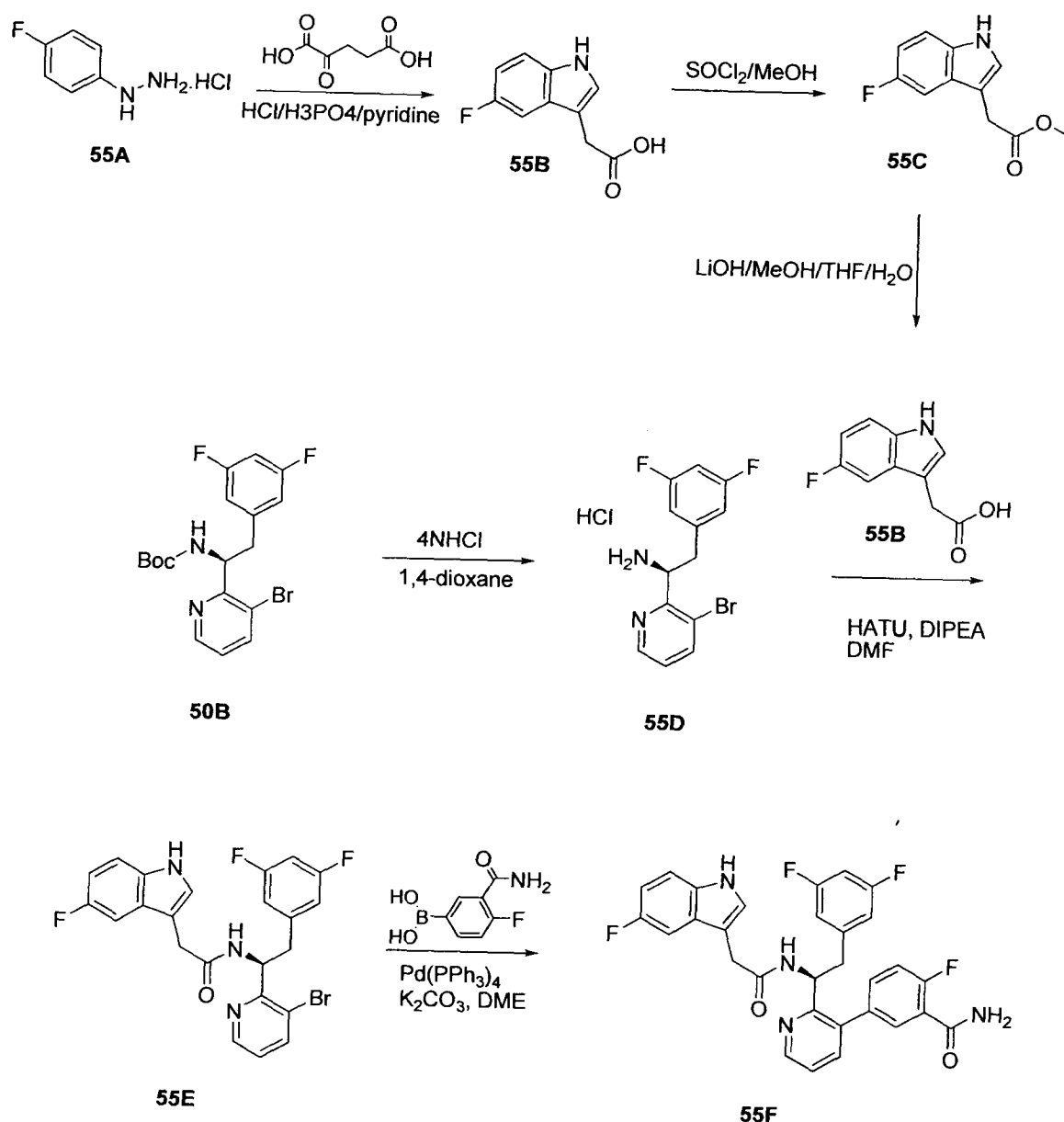
- A round bottom flask was charged with methyl 2-(5-(trifluoromethyl)-1H-indol-3-yl)acetate (1.4 g, 5.3 mmol), methanol (2 ml), and THF (6 ml). To the resulting mixture was added a solution of
25 LiOH (638 mg, 27 mmol) dissolved in water (2 ml). The mixture was stirred until done after which the mixture was diluted with ethyl acetate and the layers separated, the aqueous layer was acidified and extracted 2X with ethyl acetate and the combined organic layers were dried over sodium sulfate, filtered and concentrated to give the desired compound (1.3 g, 99%): MS (m/z) 244.1 $[M+H]^+$.

- 30 Synthesis of (S)-5-(2-(2-(3,5-difluorophenyl)-1-(2-(5-(trifluoromethyl)-1H-indol-3-yl)acetamido)ethyl)pyridin-3-yl)-2-fluorobenzamide (**54G**):

A 2 dram vial was charged with **54F** (25 mg, 0.13 mmol), **54B** (50 mg, 0.13 mmol), HATU (50 mg, 0.13 mmol), DiPEA (0.1 ml, 0.6 mmol) and DMF (1.5 ml). The mixture was stirred until

done by LC/MS then diluted with a 1:1 mixture of TFA:water (0.5 ml), filtered and purified by HPLC to afford the desired compound (16.8 mg, 28%): ^1H NMR (400 MHz, dmsO) δ 11.24 (s, 1H), 8.70 (d, 1H), 8.63 (dd, 1H), 7.80 (s, 1H), 7.63 (d, 2H), 7.56 (dd, 1H), 7.50 – 7.42 (m, 2H), 7.37 (dd, 2H), 7.31 – 7.17 (m, 3H), 6.82 (t, 1H), 6.48 (d, 2H), 5.14 (dd, 1H), 3.52 (s, 2H), 2.96 (d, 2H); MS (m/z) 597.6 $[\text{M}+\text{H}]^+$.

Example 55



Synthesis of 2-(5-fluoro-1H-indol-3-yl)acetic acid (**55B**):

To a suspension of **55A** (140 g, 861 mmol, 1.0 eq), α -ketoglutaric acid (151 g, 1.03 mol) in conc. HCl (1500 mL) and H₃PO₄ (600 mL) was added dropwise pyridine (450 mL) while keeping the temperature below 10 °C. After addition, the suspension was refluxed for 4 hours.

Upon cooling, the mixture was extracted with ether (1000 mL 5). The combined organic layer was dried with anhydrous Na₂SO₄, concentrated to afford 120g of crude title compound as a blackish green solid, which was used for the next step without any further purification.

Synthesis of Methyl 2-(5-fluoro-1H-indol-3-yl)acetate (**55C**):

- 5 To a suspension of **55B** (130 g, crude) in MeOH (1000 mL) was added dropwise SOCl₂ (120 g, 1.00 mol) while keeping the temperature below 10 °C. After addition, the suspension was refluxed for 3 hours. After cooling and concentration, the residue was diluted with DCM (1000 mL) and H₂O (500 mL). The organic layer was washed with saturated NaHCO₃ solution, dried and concentrated. The residue was purified by silica chromatography (PE/EtOAc from 50/1 to 10/1) to afford 20.5 g of the title compound as a pale solid.

Synthesis of 2-(5-fluoro-1H-indol-3-yl)acetic acid (**55B**) by saponification:

Compound **55B** was saponified by a method analogous to Example **74C**.

- 15 Synthesis of (S)-1-(3-bromopyridin-2-yl)-2-(3,5-difluorophenyl)ethanamine hydrochloride (**55D**):

Dissolved **50B** (4.4 g, 10.7 mmol) in 20 ml 4N HCl/1,4-dioxane. The reaction was stirred for 1hr at room temperature then concentrated *in vacuo*. Azeotroped residue 3x with Et₂O, then dried under vacuum to give 3.7 g of the title compound as an off white solid.

20

Synthesis of (S)-N-(1-(3-bromopyridin-2-yl)-2-(3,5-difluorophenyl)ethyl)-2-(5-fluoro-1H-indol-3-yl)acetamide (**55E**):

Dissolved **55B** (151 mg, 0.780 mmol) and **55E** (300 mg, 0.858 mmol) in DMF (8ml).

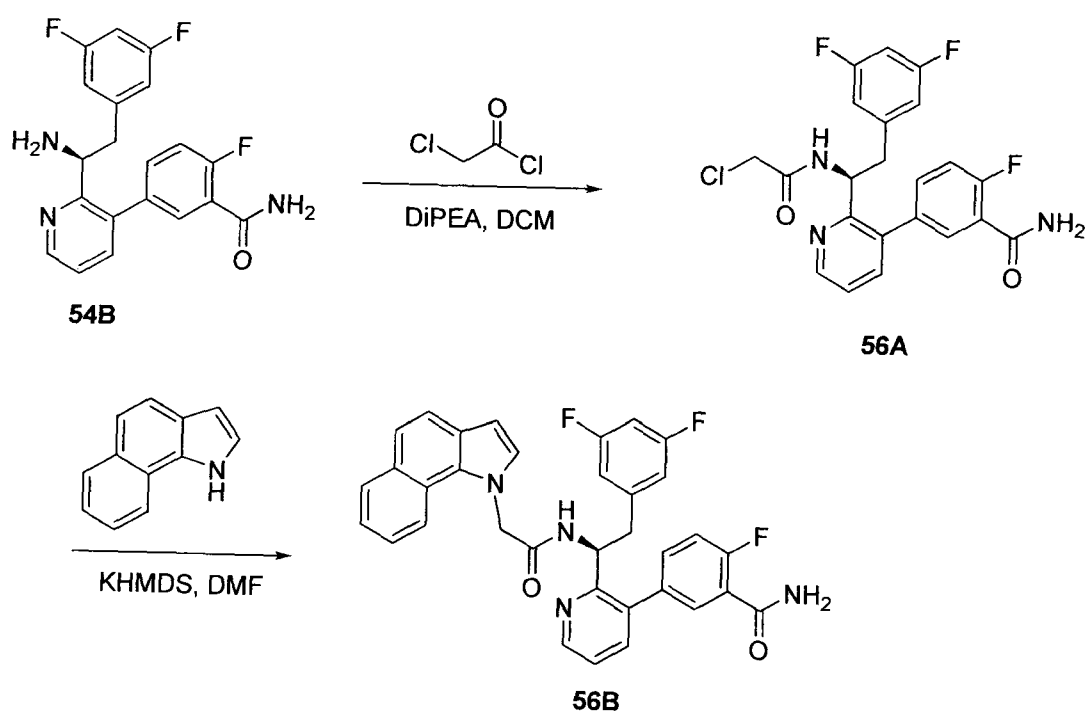
- 25 Diisopropylethylamine (791 ul, 2.57 mmol) and HATU (326 mg, 0.858 mmol) were added and the reaction was stirred at room temperature overnight. The reaction was partitioned between EtOAc and H₂O. The aqueous layer was extracted 2x EtOAc. The combined organics were washed 2x brine, dried and concentrated. Purified crude product on SiO₂ eluting with EtOAc/hexanes. Concentration of the purified fractions gave 373 mg of the title compound. MS (*m/z*) 488.7 [M+H]⁺.

30

Synthesis of (S)-5-(2-(2-(3,5-difluorophenyl)-1-(2-(5-fluoro-1H-indol-3-yl)acetamido)ethyl)pyridin-3-yl)-2-fluorobenzamide (**55**):

To a solution of **55E** (50 mg, 0.102 mmol) and 4-fluoro-3-carbamoyl phenylboronic acid (21 mg, 0.113 mmol) in DME (1 ml) was added 0.4N aq. K_2CO_3 (515 μ l) and $Pd(PPh_3)_4$ (11.9 mg, 0.0010 mmol). The resulting mixture was heated at 110 °C for 10 min. in a microwave. The reaction mixture was filtered, washed 1x with DMF and the solution was purified by RP HPLC using a C18 column with a gradient of 0.1%/H₂O, 0.1% TFA-acetonitrile, to provide 37 mg of the title compound. ¹H NMR (400 MHz, dmso) δ 10.87 (s, 1H), 8.81 – 8.53 (m, 2H), 7.66 (d, 2H), 7.56 (d, 1H), 7.47 (dd, 1H), 7.39 – 7.32 (m, 1H), 7.30 – 7.17 (m, 2H), 7.15 – 7.04 (m, 2H), 6.83 (ddd, 2H), 6.51 (d, 2H), 5.12 (dd, 1H), 3.51 – 3.31 (m, 2H), 2.98 (dd, 2H). MS (*m/z*) 547 [M+H]⁺.

Example 56



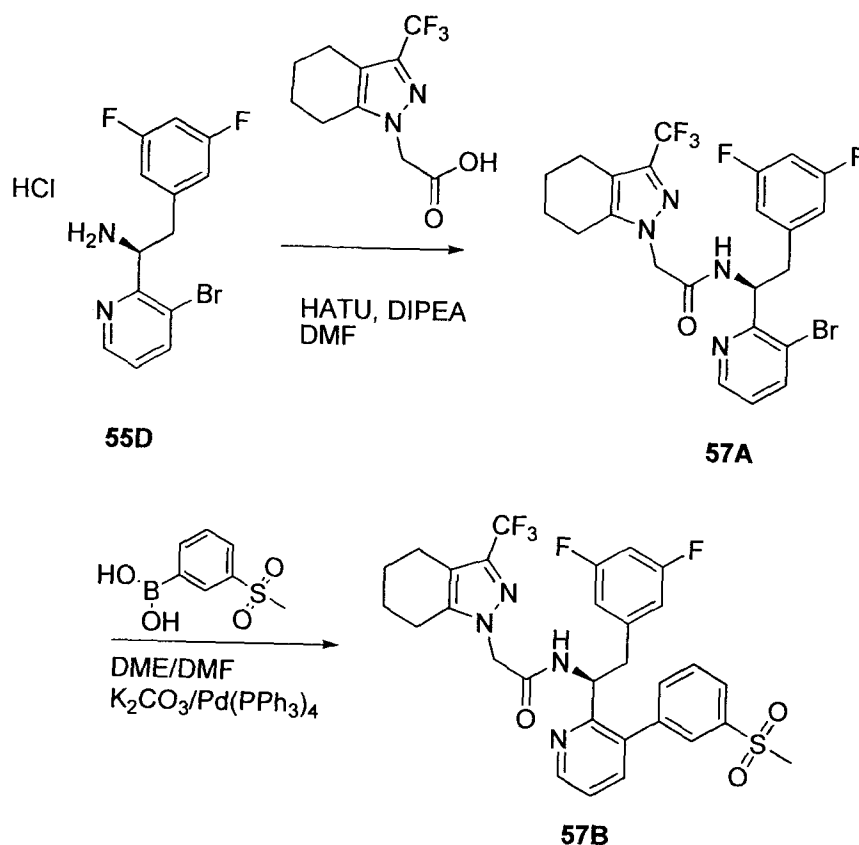
Synthesis of (S)-5-(2-(1-(2-chloroacetamido)-2-(3,5-difluorophenyl)ethyl)pyridin-3-yl)-2-fluorobenzamide (**56A**):

A round bottom flask was charged with (S)-5-(2-(1-amino-2-(3,5-difluorophenyl)ethyl)pyridin-3-yl)-2-fluorobenzamide (800 mg, 7.7 mmol), DCM (20 ml), and DiPEA (0.8 ml, 4.6 mmol). To the stirring mixture slowly add 2-chloroacetyl chloride (0.16 ml, 2 mmol) and allow to stir 30 minutes then quench with H₂O. Extract 2X DCM. The combined organic layers were dried over sodium sulfate, concentrated, and purified by flash chromatography to give the desired compound (460 mg, 61%): MS (*m/z*) 448.5 [M+H]⁺.

Synthesis of (S)-5-(2-(1-(2-(1H-benzo[g]indol-1-yl)acetamido)-2-(3,5-difluorophenyl)ethyl)pyridin-3-yl)-2-fluorobenzamide (**56B**):

A 2 dram vial was charged with 1H-benzo[g]indole (11.7 mg, 0.07 mmol), KHMDS (13.9 mg, 0.07 mmol), and DMF (1.5 ml). The resulting mixture was stirred for 10 minutes then (S)-5-(2-(1-(2-chloroacetamido)-2-(3,5-difluorophenyl)ethyl)pyridin-3-yl)-2-fluorobenzamide (30 mg, 0.07 mmol) was added. The mixture was stirred until done by LC/MS then diluted with a 1:1 mixture of TFA:water (0.5 ml), filtered and purified by HPLC to afford the desired compound (5.4 mg, 13%): ¹H NMR (400 MHz, dmso) δ 9.09 (d, 1H), 8.73 (d, 1H), 7.91 (d, 1H), 7.85 (d, 1H), 7.57 (dd, 4H), 7.40 (dd, 3H), 7.29 (d, 3H), 7.19 (dd, 2H), 6.93 (s, 1H), 6.51 (d, 3H), 5.25 (s, 2H), 5.16 (d, 1H), 3.02 (d, 2H); MS (*m/z*) 579.8 [M+H]⁺.

Example 57



Synthesis of (S)-N-(1-(3-bromopyridin-2-yl)-2-(3,5-difluorophenyl)ethyl)-2-(3-(trifluoromethyl)-4,5,6,7-tetrahydro-1H-indazol-1-yl)acetamide (**57A**):

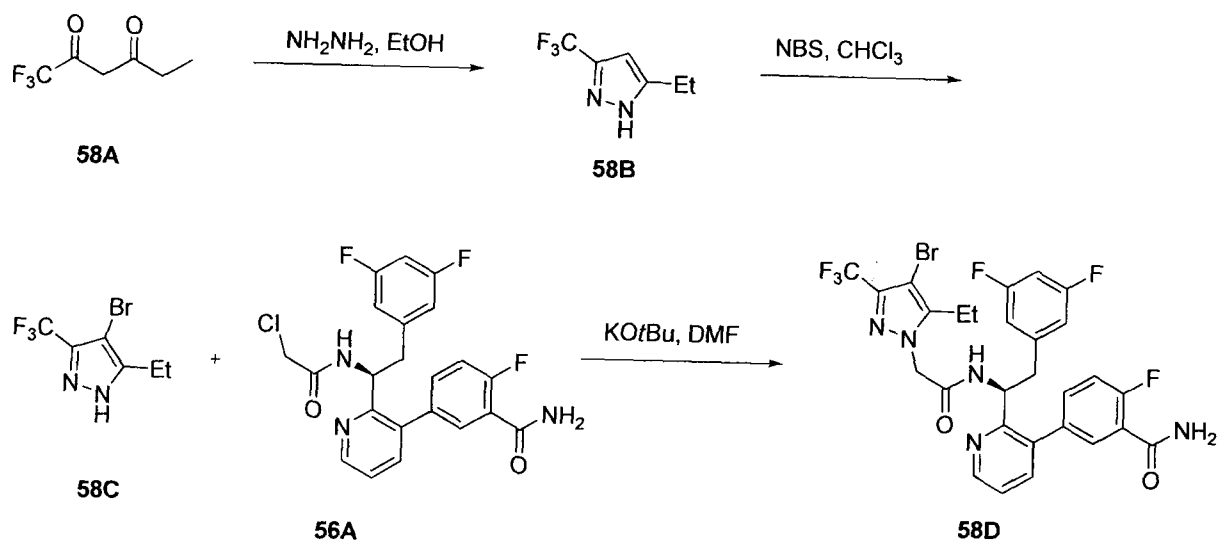
To a solution of **55D** (3.73 g, 10.7 mmol) and diisopropylethylamine (5.07 ml, 29.1 mmol) was added 2-(3-(trifluoromethyl)-4,5,6,7-tetrahydro-1H-indazol-1-yl)acetic acid (2.41 g, 9.71 mmol)

and 2-(1H-7-Azabenzotriazol-1-yl)-1,1,3,3-tetramethyl uronium hexafluorophosphate (HATU, 3.69 g, 9.71 mmol). The reaction mixture was stirred 16hrs at room temperature and then concentrated under reduce pressure. The residue was dissolved in hot CH_2Cl_2 and filtered to remove insoluble material. The filtrate was reheated and allowed to cool. The solid that formed
 5 was collected by filtration, washed with hexanes and air dried. The mother liquors were concentrated and the residue was recrystallized from EtOAc/hexanes. Recovered a total of 4.2 g of the title compound. MS (m/z) 544.7 $[\text{M}+\text{H}]^+$.

Synthesis of (S)-N-(2-(3,5-difluorophenyl)-1-(3-(3-(methylsulfonyl)phenyl)pyridin-2-yl)ethyl)-
 10 2-(3-(trifluoromethyl)-4,5,6,7-tetrahydro-1H-indazol-1-yl)acetamide (**57B**):

Dissolved **57A** (49.4 mg, 0.091 mmol) and 3-methylsulfonylphenyl boronic acid (20 mg, 0.1 mmol) in 4:1 DMEDMF (1ml). Added 2N aq. K_2CO_3 (100 ul) and $\text{Pd}(\text{PPh}_3)_4$ (12 mg, 0.01 mmol) and then heated the reaction at 100 °C under N_2 for 16 hrs. The reactions were cooled, diluted with H_2O and extracted with EtOAc (2x). The organic layer was concentrated under
 15 reduced pressure. The residue was purified by RP HPLC using a C18 column with a gradient of 0.1%/H₂O, 0.1% TFA-acetonitrile to give 2.6 mg of the title compound. MS (m/z) 619 $[\text{M}+\text{H}]^+$.

Example 58



Synthesis of 5-ethyl-3-(trifluoromethyl)-1H-pyrazole (**58B**):

To a solution of 1,1,1-trifluorohexane-2,4-dione (8.4 g, 50 mmol) in EtOH (100 mL) was slowly added hydrazine hydrate (5.0 g, 50 mmol). The reaction was stirred at room temperature for 1 h

and then heated to reflux for 1 h. The reaction was cooled to room temperature and the solvent was removed in vacuo to give 8 g of the title compound. MS (m/z): 165.0 [M+H]⁺; HPLC retention time 0.77 min (2-98% acetonitrile: water with 0.05% trifluoroacetic acid).

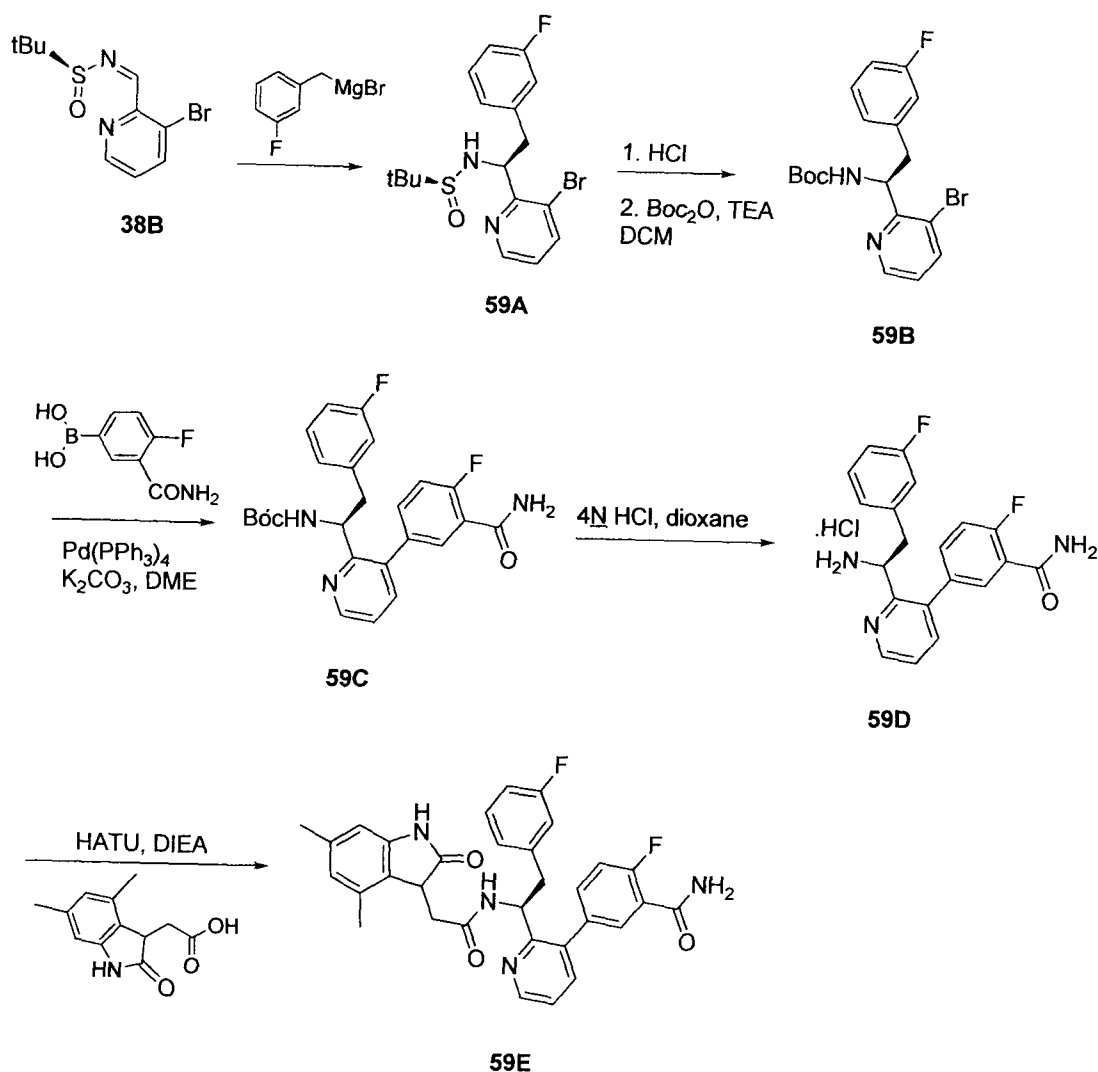
5 Synthesis of 4-bromo-5-ethyl-3-(trifluoromethyl)-1H-pyrazole (**58C**):

To a solution of 5-ethyl-3-(trifluoromethyl)-1H-pyrazole (3.3 g, 20 mmol) in CHCl₃ (100 mL) was added NBS (4.3 g, 24 mmol). The reaction was stirred at room temperature overnight and was then poured into ethyl acetate and washed with saturated Na₂S₂O₃ solution and brine. The organic layer was dried over sodium sulfate, filtered and concentrated. The resulting residue
10 was purified by silica gel chromatography eluting with EtOAc / hexanes to afford 4.8 g of the title product. MS (m/z): 243.1 [M+H]⁺; HPLC retention time 0.98 min (2-98% acetonitrile: water with 0.05% trifluoroacetic acid).

15 Synthesis of (S)-5-(2-(1-(2-(4-bromo-5-ethyl-3-(trifluoromethyl)-1H-pyrazol-1-yl)acetamido)-2-(3,5-difluorophenyl)ethyl)pyridin-3-yl)-2-fluorobenzamide (**58D**):

To a solution of 4-bromo-5-ethyl-3-(trifluoromethyl)-1H-pyrazole (290 mg, 1.2 mmol) in DMF (5 mL) was added potassium tert-butoxide (168 mg, 1.5 mmol) at room temperature. After stirred at rt for 10 min, (S)-5-(2-(1-(2-chloroacetamido)-2-(3,5-difluorophenyl)ethyl)pyridin-3-yl)-2-fluorobenzamide (447 mg, 1 mmol) was added in one portion. The reaction was stirred at
20 room temperature for 1 h and was then poured into ethyl acetate and washed with saturated NH₄Cl solution and brine. The organic layer was dried over sodium sulfate, filtered and concentrated. The resulting residue was purified by silica gel chromatography eluting with EtOAc / hexanes to afford 430 mg of the title product. MS (m/z): 656.1 [M+H]⁺; HPLC retention time 1.22 min (2-98% acetonitrile: water with 0.05% trifluoroacetic acid). ¹H NMR
25 (400 MHz, cdcl₃) δ 8.56 (s, 1H), 7.61 (d, J = 5.1 Hz, 1H), 7.50 (s, 1H), 7.31 (s, 1H), 7.29 – 7.13 (m, 3H), 6.75 (s, 1H), 6.55 (s, 1H), 6.12 (d, J = 6.4 Hz, 2H), 5.79 (s, 1H), 5.43 (d, J = 7.4 Hz, 1H), 4.79 (d, J = 3.5 Hz, 2H), 2.87 (m, 2H), 2.65 (q, J = 7.6 Hz, 2H), 1.09 (t, J = 7.6 Hz, 3H).

Example 59



Synthesis of (S)-N-((S)-1-(3-bromopyridin-2-yl)-2-(3-fluorophenyl)ethyl)-2-methylpropane-2-sulfinamide (**59A**):

Compound **59A** was prepared according to the method presented for the synthesis of Example 38 substituting (3-fluorobenzyl)magnesium chloride for (3,5-difluorobenzyl)magnesium bromide and **38B** to provide of 1.2 g of title compound. MS (m/z) 399 $[\text{M}+\text{H}]^+$.

Synthesis of (S)-tert-butyl (1-(3-(3-carbamoyl-4-fluorophenyl)pyridin-2-yl)-2-(3-fluorophenyl)ethyl) carbamate (**59B**):

Compound **59B** was prepared according to the method presented for the synthesis of Example 50 substituting **59A** for **38C** to provide 0.5 g of title compound: MS (m/z) 395 $[\text{M}+\text{H}]^+$.

Synthesis of (S)-tert-butyl (1-(3-(3-carbamoyl-4-fluorophenyl)pyridin-2-yl)-2-(3-fluorophenyl)ethyl)carbamate (**59C**):

Compound 59C was prepared according to the method presented for the synthesis of Example 50 utilizing **59B** for **50A** and (3-carbamoyl-4-fluorophenyl)boronic acid to provide 450 mg of title compound: MS (m/z) 454 $[M+H]^+$.

5 Synthesis of (S)-5-(2-(1-amino-2-(3-fluorophenyl)ethyl)pyridin-3-yl)-2-fluorobenzamide hydrochloride (**59D**):

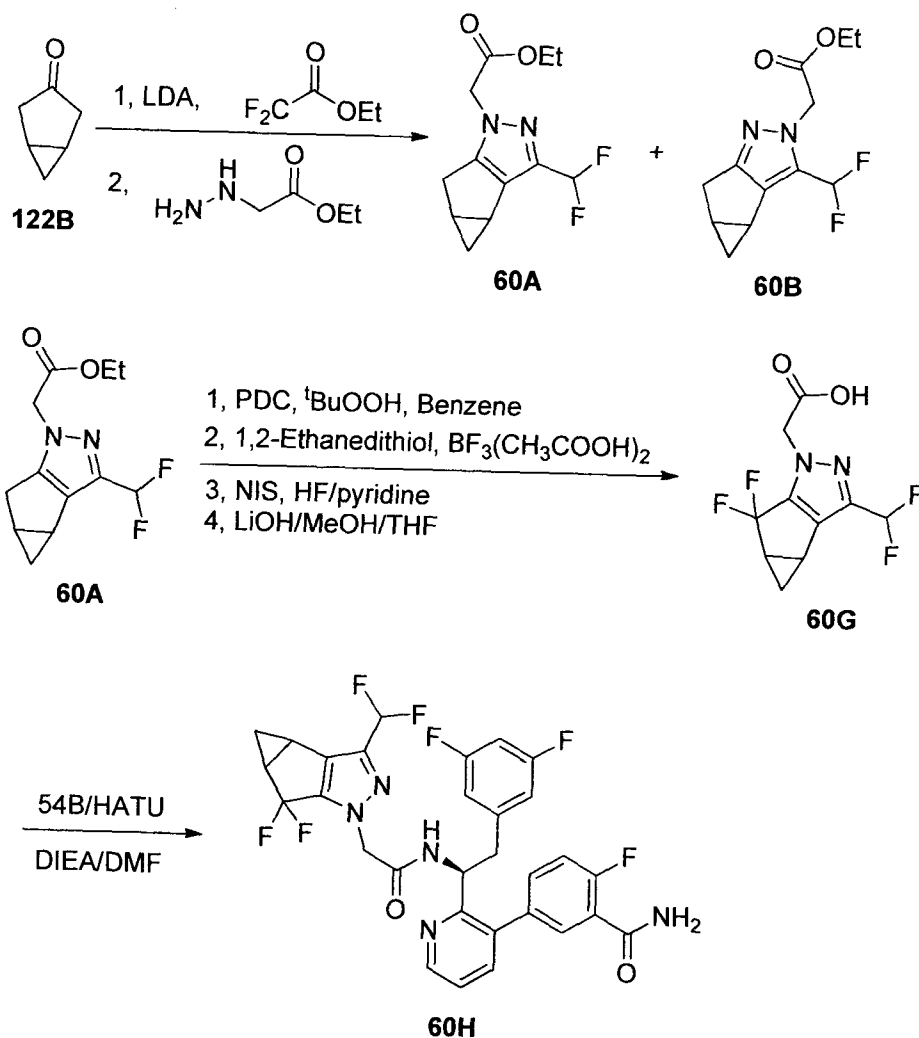
4N HCl/1,4-dioxane (5.0 ml) was added to **59C** (0.45 g, 10 mmol). LC/Mass showed completion of reaction after 10 min. Concentrated reaction mixture *in vacuo* to give 360 mg of title compound: MS (m/z) 354 $[M+H]^+$.

10

Synthesis of 5-(2-((1S)-1-(2-(4,6-dimethyl-2-oxoindolin-3-yl)acetamido)-2-(3-fluorophenyl)ethyl)pyridin-3-yl)-2-fluorobenzamide (**59E**):

Combined **59D** (36 mg, 0.1 mmol), 2-(4,6-dimethyl-2-oxoindolin-3-yl)acetic acid (22 mg, 0.1 mmol) and HATU (38 mg, 0.1 mmol) in 1ml vial. Added DMF and stirred to dissolve the solids. Added diisopropylethylamine (45 ul, 0.26 mmol) and stirred reaction at room temperature for 90 min. LC/MS shows desired product with a small amount of acid. Purified reaction mixture on prep reverse phase HPLC using 20-80%B over 20 min. (A=0.1%TFA/H₂O;B=0.1%TFA/Acetonitrile). Combined pure fractions as determined by LC/MS and lyophilized to provide 35 mg of title compound. ¹H NMR (400 MHz, cd₃od) δ 8.63 (ddd, 2H), 7.67 (dd, 1H), 7.58 (dd, 1H), 7.51 – 7.09 (m, 8H), 7.14 (s, 1H), 7.16 – 6.95 (m, 3H), 6.81 (dd, 2H), 6.69 (d, 2H), 6.57 (d, 2H), 6.53 – 6.32 (m, 4H), 5.27 (dd, 2H), 3.95 (d, 2H), 3.05 – 2.76 (m, 6H), 2.76 – 2.59 (m, 3H), 2.34 (s, 1H), 2.24 (d, 5H), 2.14 (d, 5H).; MS (m/z) 555 $[M+H]^+$.

25 Example 60



Synthesis of ethyl 2-(3-(difluoromethyl)-3b,4,4a,5-tetrahydro-1H-

5 cyclopropa[3,4]cyclopenta[1,2-c]pyrazol-1-yl)acetate (**60A**) and ethyl 2-(3-(difluoromethyl)-3b,4,4a,5-tetrahydro-2H-cyclopropa[3,4]cyclopenta[1,2-c]pyrazol-2-yl)acetate (**60B**):

Compound 60A and 60B were prepared according to the method presented for the synthesis of Example 122 substituting ethyl 2,2-difluoroacetate for ethyl 2,2,2-trifluoroacetate to provide 1.7 g of **60A** and 0.33 g of **60B**. **60A**: MS (*m/z*) 257 [M+H]⁺ and **60B**: MS (*m/z*) 257 [M+H]⁺.

Synthesis of 2-(3-(difluoromethyl)-5,5-difluoro-3b,4,4a,5-tetrahydro-1H-cyclopropa[3,4]cyclopenta[1,2-c]pyrazol-1-yl)acetic acid (**60G**):

Compound 60G was prepared according to the method presented for the synthesis of Example 181 substituting **60A** for **122D** to provide 140 mg of title compound. MS (*m/z*) 265 [M+H]⁺.

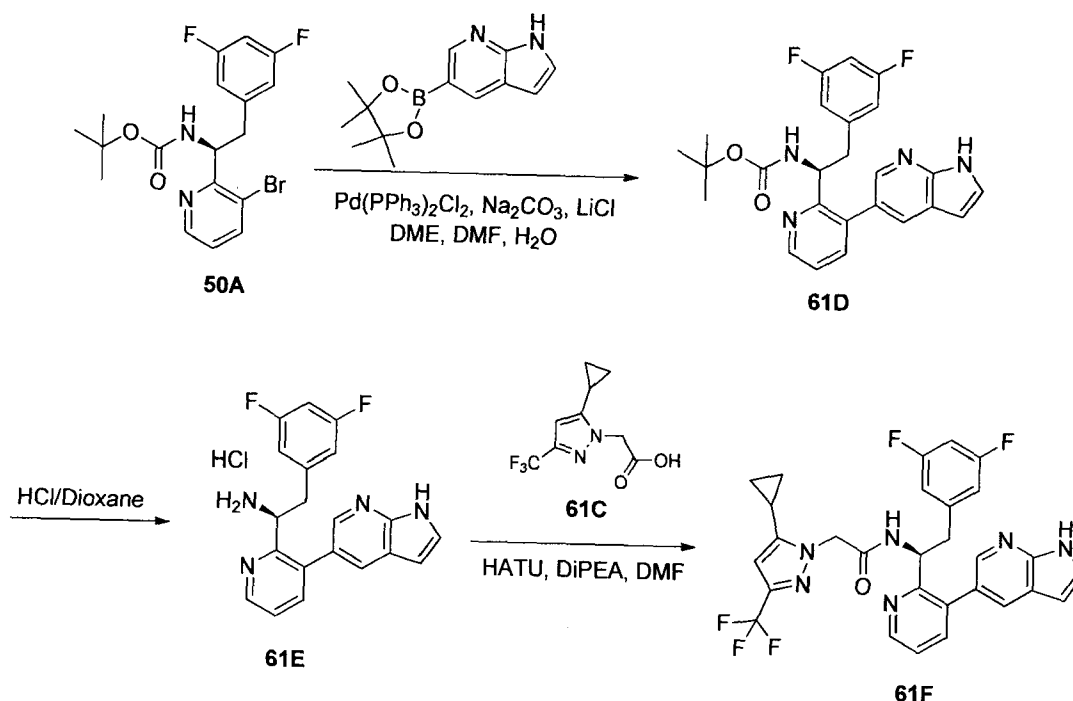
Synthesis of 5-(2-((1S)-1-(2-(3-(difluoromethyl)-5,5-difluoro-3b,4,4a,5-tetrahydro-1H-cyclopropa[3,4]cyclopenta[1,2-c]pyrazol-1-yl)acetamido)-2-(3,5-difluorophenyl)ethyl)pyridin-3-yl)-2-fluorobenzamide (**60H**):

Compound **60H** was prepared according to the method presented for the synthesis of Example

5 54 utilizing **54B** and **60G** to provide 254 mg of title compound: ^1H NMR (400 MHz, cd_3od) δ 8.66 (dd, 1H), 7.54 (ddd, 1.7 Hz, 1H), 7.27 (dddd, 4H), 6.82 (d, 1H), 6.73 – 6.57 (m, 2H), 6.54 (d, 1H), 6.37 – 6.19 (m, 2H), 5.42 – 5.27 (m, 1H), 4.39 – 4.22 (m, 1H), 4.07 (q, 1H), 3.23 – 2.91 (m, 2H), 2.51 – 2.38 (m, 2H), 1.98 (s, 1H), 1.82 (s, 1H), 1.97 – 1.17 (m, 4H), 1.15 – 0.97 (m, 1H), 0.89 (t, 1H). MS (m/z) 618 [$\text{M}+\text{H}$] $^+$.

10

Example 61



Synthesis of (S)-tert-butyl 1-(3-(1H-pyrrolo[2,3-b]pyridin-5-yl)pyridin-2-yl)-2-(3,5-difluorophenyl)ethylcarbamate (**61D**):

15 A round bottom flask was charged with **50A** (1 g, 2.4 mmol), DME (8 ml), DMF (2 ml), 5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrrolo[2,3-b]pyridine (886 mg, 3.6 mmol), LiCl (308 mg, 7.2 mmol), $\text{Pd}(\text{PPh}_3)_2\text{Cl}_2$ (85 mg, 0.12 mmol) and Na_2CO_3 (513 mg, 4.8 mmol) dissolved in water (2 ml). Microwave the reaction at 150 $^\circ\text{C}$ for 20 minutes.. Allow the reaction to cool then dilute with H_2O and extract 2X EtOAc. The combined organic layers were washed

20 with brine then dried over sodium sulfate, concentrated, and purified by flash chromatography to give the desired compound (785 mg, 72%): MS (m/z) 451.3 [$\text{M}+\text{H}$] $^+$.

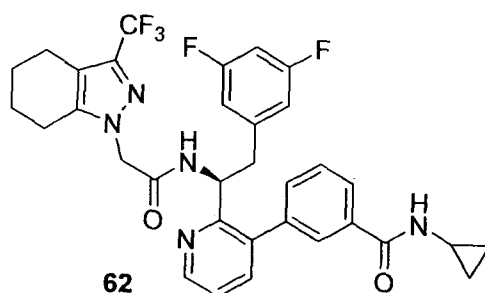
Synthesis of (S)-1-(3-(1H-pyrrolo[2,3-b]pyridin-5-yl)pyridin-2-yl)-2-(3,5-difluorophenyl)ethanamine hydrochloride (**61E**):

A round bottom flask was charged with (S)-tert-butyl 1-(3-(1H-pyrrolo[2,3-b]pyridin-5-yl)pyridin-2-yl)-2-(3,5-difluorophenyl)ethylcarbamate (549 mg, 1.2 mmol) and 4 N HCl/dioxane (3 ml). The reaction was stirred at room temperature until done by LC/MS then concentrated 2X from DCM. The crude solid was used as is in next reaction: MS (m/z) 351.2 $[M+H]^+$.

Synthesis of (S)-N-(1-(3-(1H-pyrrolo[2,3-b]pyridin-5-yl)pyridin-2-yl)-2-(3,5-difluorophenyl)ethyl)-2-(5-cyclopropyl-3-(trifluoromethyl)-1H-pyrazol-1-yl)acetamide (**61F**):

The title compound was prepared according to the method presented in the synthesis of **34E** substituting **61C** for **34D** and **61E** for (S)-2-(3,5-difluorophenyl)-1-(3-(4-methoxyphenyl)pyridin-2-yl)ethanamine to provide the desired compound (16.8 mg, 33%): ^1H NMR (400 MHz, cd_3od) δ 8.72 (d, 1H), 8.01 (s, 1H), 7.85 (s, 1H), 7.66 (d, 1H), 7.56 (d, 1H), 7.44 (dd, 4.8 Hz, 1H), 6.70 (s, 1H), 6.62 (d, 1H), 6.28 (d, 2H), 6.23 (s, 1H), 5.42 – 5.20 (m, 1H), 4.99 (s, 2H), 4.82 – 4.88 (m, 1H), 3.46 (s, 1H), 3.12 – 2.99 (m, 2H), 1.63 (s, 1H), 0.94 – 0.84 (m, 2H), 0.63 (s, 2H); MS (m/z) 567.5 $[M+H]^+$.

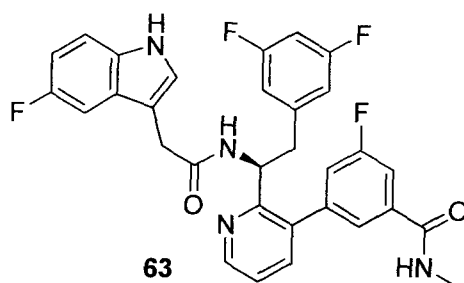
Example 62



Synthesis of (S)-N-cyclopropyl-3-(2-(2-(3,5-difluorophenyl)-1-(2-(3-(trifluoromethyl)-4,5,6,7-tetrahydro-1H-indazol-1-yl)acetamido)ethyl)pyridin-3-yl)benzamide (**62**):

Prepared 29 mg of the title compound by a method analogous to compound **57B** using **57A** and 3-(cyclopropylcarbamoyl)phenylboronic acid. MS (m/z) 624 $[M+H]^+$.

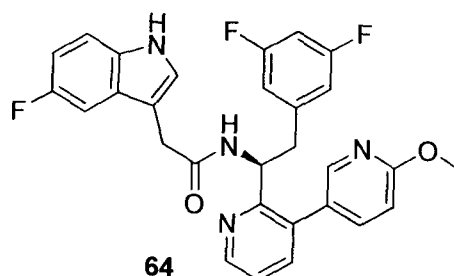
Example 63



Synthesis of (S)-3-(2-(2-(3,5-difluorophenyl)-1-(2-(5-fluoro-1H-indol-3-yl)acetamido)ethyl)pyridin-3-yl)-5-fluoro-N-methylbenzamide (**63**):

- 5 Prepared 16 mg of the title compound by a method analogous to **55F** using 3-fluoro-5-(methylcarbamoyl)phenylboronic acid and **55E**. MS (m/z) 561 $[M+H]^+$.

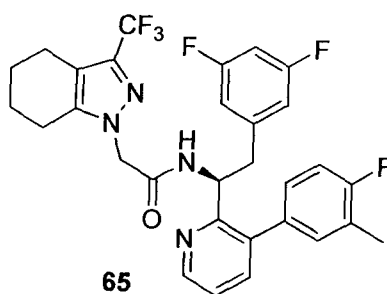
Example 64



- 10 Synthesis of (S)-N-(2-(3,5-difluorophenyl)-1-(6'-methoxy-3,3'-bipyridin-2-yl)ethyl)-2-(5-fluoro-1H-indol-3-yl)acetamide (**64**):

Prepared 22 mg of the title compound by a method analogous to **55F** using 6-methoxypyridin-3-ylboronic acid and **55E**. MS (m/z) 544 $[M+H]^+$.

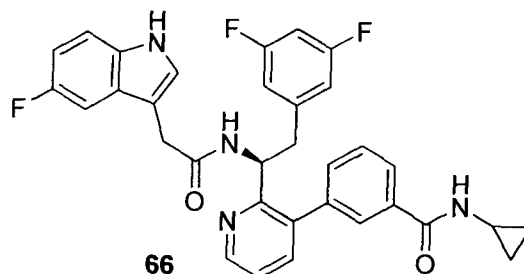
15 Example 65



Synthesis of (S)-N-(2-(3,5-difluorophenyl)-1-(3-(4-fluoro-3-methylphenyl)pyridin-2-yl)ethyl)-2-(3-(trifluoromethyl)-4,5,6,7-tetrahydro-1H-indazol-1-yl)acetamide (**65**):

Prepared 33.5 mg of the title compound by a method analogous to compound **57B** using **57A** and 3-methyl-4-fluorophenyl boronic acid. MS (m/z) 573 $[M+H]^+$.

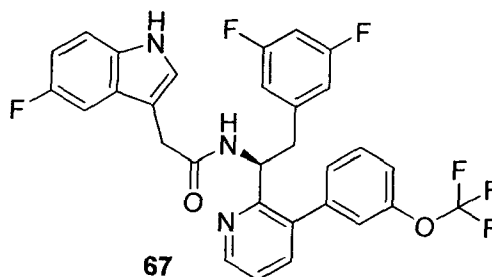
Example 66



Synthesis of (S)-N-cyclopropyl-3-(2-(2-(3,5-difluorophenyl)-1-(2-(5-fluoro-1H-indol-3-yl)acetamido)ethyl)pyridin-3-yl)benzamide (**66**):

Prepared 1.5 mg of the title compound by a method analogous to **55F** using [3-(cyclopropylaminocarbonyl)phenyl] boronic acid and **55E**. MS (m/z) 569 $[M+H]^+$.

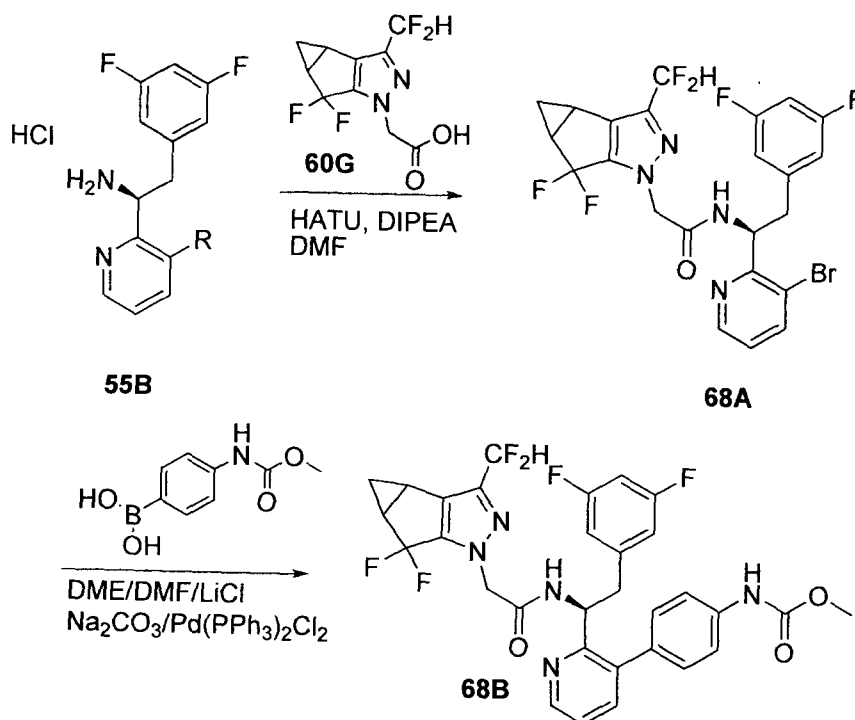
Example 67



Synthesis of (S)-N-(2-(3,5-difluorophenyl)-1-(3-(3-(trifluoromethoxy)phenyl)pyridin-2-yl)ethyl)-2-(5-fluoro-1H-indol-3-yl)acetamide (**67**):

Prepared 34.9 mg of the title compound by a method analogous to **55F** using 3-trifluoromethoxy-phenylboronic acid and **55E**. MS (m/z) 570 $[M+H]^+$.

Example 68



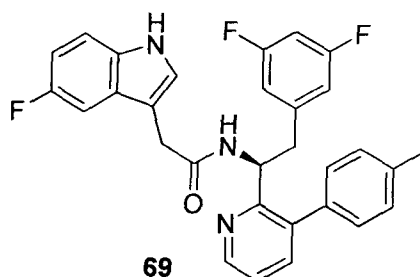
Synthesis of (S)-N-(1-(3-bromo-pyridin-2-yl)-2-(3,5-difluorophenyl)ethyl)-2-(3-(difluoromethyl)-5,6-dihydro-4,5-(methano)-6,6-difluoro-cyclopenta[c]pyrazol-1(4H)-yl)acetamide (**68A**):

- 5 Prepared 1.5g of the title compound by a method analogous to **55E** using **60G** and **55B**. MS (m/z) 560 $[\text{M}+\text{H}]^+$.

Synthesis of (S)-methyl 4-(2-(1-(3-(difluoromethyl)-5,6-dihydro-4,5-(methano)-6,6-difluoro-cyclopenta[c]pyrazol-1(4H)-yl)acetamido)-2-(3,5-difluorophenyl)ethyl)pyridin-3-yl)phenylcarbamate (**68B**):

- 10 To a solution of **68A** (28 mg, 0.05 mmol) and (4-(methoxycarbonylamino)phenyl)boronic acid (19.5 mg, 0.1 mmol) in 4:1 DME/DMF (500ul) was added LiCl (6.4 mg, 0.15 mmol), 1N aq. Na_2CO_3 (125ul, 0.125 mmol), and $\text{Pd(PPh}_3)_2\text{Cl}_2$ (7 mg, 0.01 mmol). The reaction was heated in a microwave synthesizer at 150 °C for 15 min. The cooled suspension was filtered and the filtrate
- 15 was purified by RP HPLC using a C18 column with a gradient of 0.1%/H₂O, 0.1% TFA-acetonitrile to give 18.5 mg of the title compound. MS (m/z) 630 $[\text{M}+\text{H}]^+$.

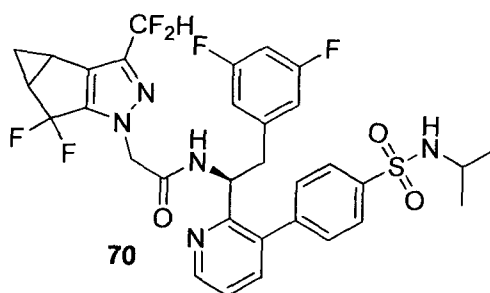
Example 69



Synthesis of (S)-N-(2-(3,5-difluorophenyl)-1-(3-(4-methylphenyl)pyridin-2-yl)ethyl)-2-(5-fluoro-1H-indol-3-yl)acetamide (**69**):

Prepared 36.3 mg of the title compound by a method analogous to **55F** using 4-methylphenylboronic acid and **55E**. MS (m/z) 500 $[M+H]^+$.

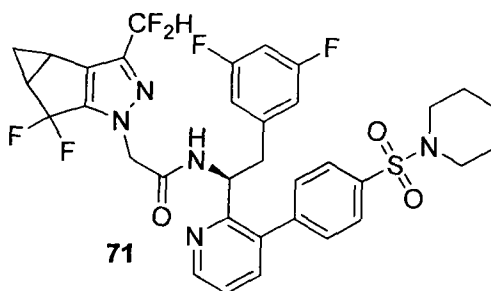
Example 70



Synthesis of (S)-N-(1-(3-(4-(N-isopropylsulfonyl)phenyl)-pyridin-2-yl)-2-(3,5-difluorophenyl)ethyl)-2-(3-(difluoromethyl)-5,6-dihydro-4,5-(methano)-6,6-difluorocyclopenta[c]pyrazol-1(4H)-yl)acetamide (**70**):

Prepared 8.4 mg of the title compound by a method analogous to **68B** using **68A** and N-isopropyl 4-boronobenzenesulfonamide. MS (m/z) 678 $[M+H]^+$.

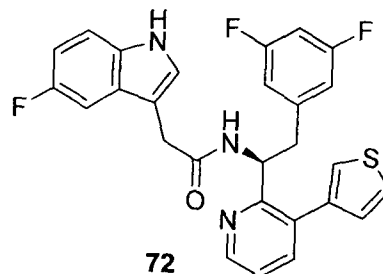
Example 71



Synthesis of (S)-N-(1-(3-(4-((piperidin-1-yl)sulfonyl)phenyl)-pyridin-2-yl)-2-(3,5-difluorophenyl)ethyl)-2-(3-(difluoromethyl)-5,6-dihydro-4,5-(methano)-6,6-difluorocyclopenta[c]pyrazol-1(4H)-yl)acetamide (**71**):

Prepared 14.8 mg of the title compound by a method analogous to **68B** using **68A** and 4-(piperidin-1-ylsulfonyl)phenylboronic acid. MS (m/z) 704 $[M+H]^+$.

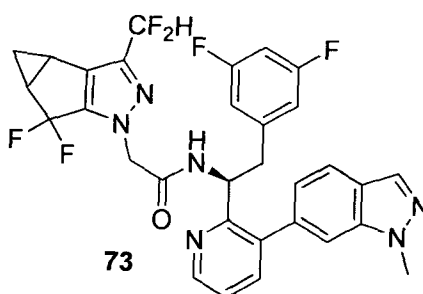
Example 72



Synthesis of (S)-N-(2-(3,5-difluorophenyl)-1-(3-(thiophen-3-yl)pyridin-2-yl)ethyl)-2-(5-fluoro-1H-indol-3-yl)acetamide (**72**):

Prepared 29 mg of the title compound by analogous method to **55F** using thiophen-3-yl-boronic acid and **55E**. MS (m/z) 492 $[M+H]^+$.

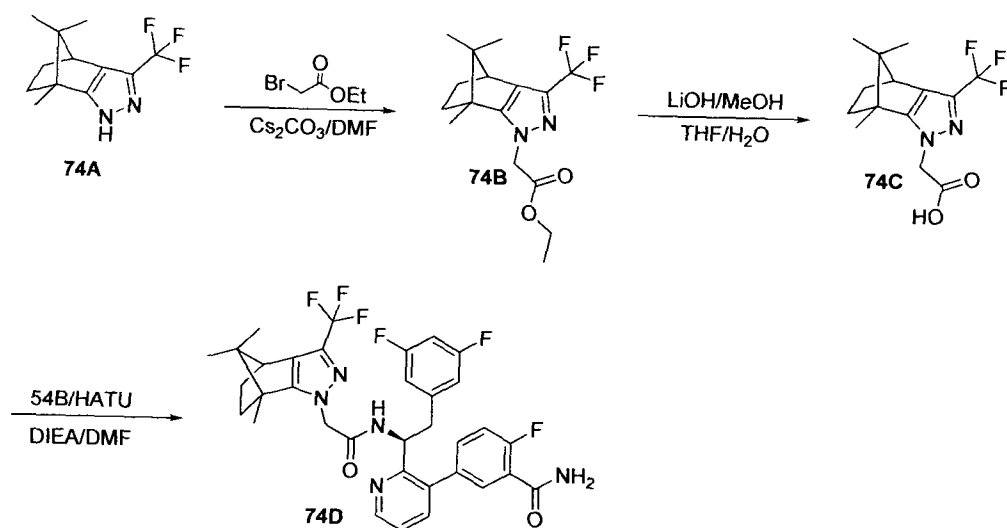
Example 73



Synthesis of (S)-N-(1-(3-(1-methylindazole-6-yl)-pyridin-2-yl)-2-(3,5-difluorophenyl)ethyl)-2-(3-(difluoromethyl)-5,6-dihydro-4,5-(methano)-6,6-difluoro-cyclopenta[c]pyrazol-1(4H)-yl)acetamide (**73**):

Prepared 21.1 mg of the title compound by a method analogous to **68B** using **68A** and 1-methylindazole-6-boronic acid. MS (m/z) 611 $[M+H]^+$.

Example 74



Synthesis of ethyl 2-(L-4,5,6,7-Tetrahydro-3-trifluoromethyl-7,8,8-trimethyl-1H-4,7-(methano)indazol-1-yl)acetate (**74B**):

- 5 To a suspension of L-4,5,6,7-tetrahydro-3-trifluoromethyl-7,8,8-trimethyl-1H-4,7-(methano)indazole (977 mg, 4 mmol), Cs_2CO_3 (1.6g, 8.3 mmol) in DMF (6 ml) was added ethyl bromoacetate as a solution in 5ml of DMF. The reaction was stirred at room temperature for 5hrs, then diluted with water. The mixture was extracted with EtOAc. The organics were dried over Na_2SO_4 , filtered and concentrated. The crude product was purified by SiO_2
- 10 chromatography eluting with a gradient of EtOAc in hexanes. Concentrated pure fractions to give 300 mg of the title compound.

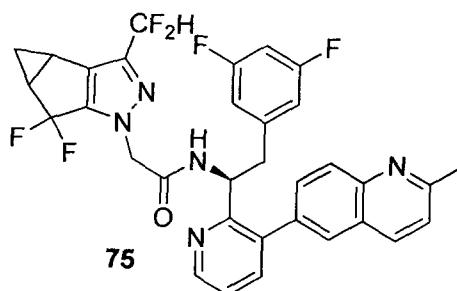
Synthesis of L-4,5,6,7-Tetrahydro-3-trifluoromethyl-7,8,8-trimethyl-1H-4,7-(methano)indazol-1-yl)acetic acid (**74C**):

- 15 Dissolved **74B** (300 mg, 0.908 mmol) in THF (5 ml) and MeOH (2.5 ml). Added 2.5ml of 2.5N aq. LiOH and stirred the reaction for 30min. at room temperature. The mixture was then acidified to pH = 3 with 1N aq. HCl and extracted 3x with EtOAc. The combined organics were washed with brine, dried over MgSO_4 , filtered and concentrated. Obtained 265 mg of the title compound after drying overnight under vacuum.
- 20 Synthesis of (S)-5-(2-(2-(3,5-difluorophenyl)-1-(2-(L-4,5,6,7-Tetrahydro-3-trifluoromethyl-7,8,8-trimethyl-1H-4,7-(methano)indazol-1-yl)acetamido)ethyl)pyridin-3-yl)-2-fluorobenzamide (**74D**):

Prepared 60 mg of the title compound by a method analogous to **54G** using **74C** and **54B**. ^1H NMR (400 MHz, CD_3OD) δ 8.71 (dd, 1H), 7.67 (dd, 1H), 7.49 – 7.40 (m, 2H), 7.30 (s, 1H), 7.27

– 7.20 (m, 1H), 6.69 (t, 1H), 6.36 (d, 2H), 5.37 (t, 1H), 3.08 (d, 2H), 2.86 (d, 1H), 2.10 (d, 1H), 1.78 (t, 1H), 1.30 (t, 1H), 1.20 (s, 3H), 1.07 (s, 1H), 0.92 (s, 3H), 0.71 (s, 3H). MS (m/z) 656 $[M+H]^+$.

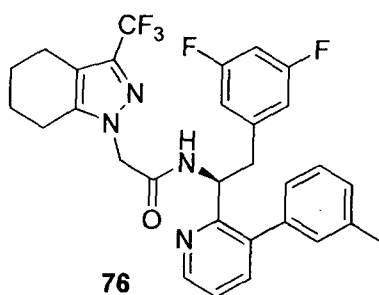
5 Example 75



Synthesis of (S)-N-(1-(3-(2-methylquinoline-6-yl)-pyridin-2-yl)-2-(3,5-difluorophenyl)ethyl)-2-(3-(difluoromethyl)-5,6-dihydro-4,5-(methano)-6,6-difluoro-cyclopenta[c]pyrazol-1(4H)-yl)acetamide (**75**):

Prepared 16.1 mg of the title compound by a method analogous to **68B** using **68A** and 2-methylquinoline-6-boronic acid pinacol ester. MS (m/z) 622 $[M+H]^+$.

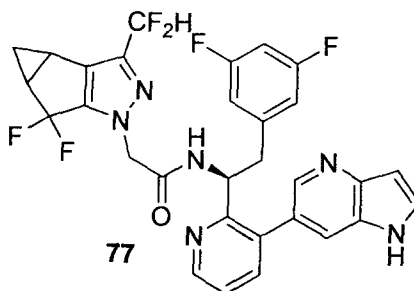
Example 76



Synthesis of (S)-N-(2-(3,5-difluorophenyl)-1-(3-m-tolylpyridin-2-yl)ethyl)-2-(3-(trifluoromethyl)-4,5,6,7-tetrahydro-1H-indazol-1-yl)acetamide (**76**):

Prepared 11.4 mg of the title compound by a method analogous to compound **57B** using **57A** and 3-methylphenyl boronic acid. MS (m/z) 555 $[M+H]^+$.

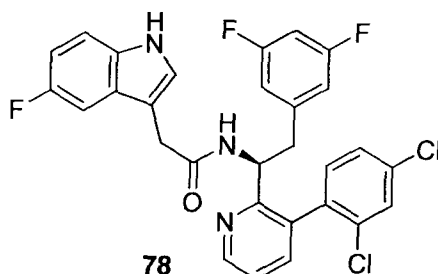
Example 77



Synthesis of (S)-N-(1-(3-(1H-pyrrolo[3,2-b]pyridine-6-yl)-pyridin-2-yl)-2-(3,5-difluorophenyl)ethyl)-2-(3-(difluoromethyl)-5,6-dihydro-4,5-(methano)-6,6-difluorocyclopenta[c]pyrazol-1(4H)-yl)acetamide (**77**):

- 5 Prepared 17.4 mg of the title compound by a method analogous to **68B** using **68A** and 6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrrolo[3,2-b]pyridine. MS (m/z) 597 $[M+H]^+$.

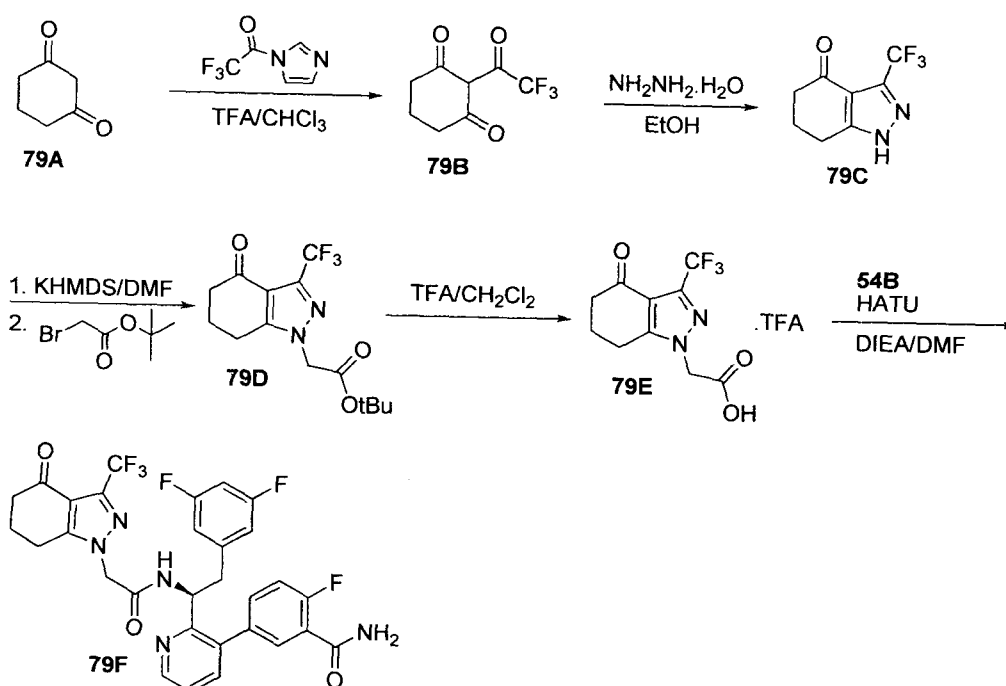
Example 78



10 Synthesis of (S)-N-(1-(3-(2,4-dichlorophenyl)pyridin-2-yl)-2-(3,5-difluorophenyl)ethyl)-2-(5-fluoro-1H-indol-3-yl)acetamide (**78**):

Prepared 19.8 mg of the title compound by a method analogous to **55F** using (2,4-dichlorophenyl)-boronic acid and **55E**. MS (m/z) 555 $[M+H]^+$.

Example 79



Synthesis of 2-(2,2,2-trifluoroacetyl)cyclohexane-1,3-dione (**79B**):

To a solution of 1,3-cyclohexanedione (561 mg, 5.0 mmol) and imidazole (340 mg, 5.0 mmol) in CH_2Cl_2 (50 ml) was added neat N-trifluoroacetyl imidazole (2.27 ml, 20 mmol). The reaction mixture was stirred at room temperature for 45min. The reaction was diluted with 4N aq. HCl and the layers were separated. The aqueous layer was extracted 2x CH_2Cl_2 . The combined organics were washed with H_2O and brine. The organics were dried over MgSO_4 , filtered and concentrated. The crude product was used directly for the next step.

Synthesis of 3-(trifluoromethyl)-6,7-dihydro-1H-indazol-4(5H)-one (**79C**):

To a solution of crude **79B** in EtOH (5 ml) was added hydrazine hydrate (500 μl , 7.8 mmol). The reaction was heated at 70°C for 2.5hrs and then concentrated under reduced pressure. The crude product was used directly for the next step.

Synthesis of tert-butyl 2-(4-oxo-3-(trifluoromethyl)-4,5,6,7-tetrahydro-1H-indazol-1-yl)acetate (**79D**):

To a solution of crude **79C** in DMF (25 ml) was added potassium hexamethyldisilazane (997 mg, 5 mmol). The reaction mixture was stirred for 2 min. at room temperature and then neat alpha-bromo-t-butylacetate was added. The reaction was stirred 1hr at room temperature and then concentrated under reduced pressure. The residue was portioned between EtOAc and H_2O . The aqueous was extracted 2x EtOAc . The combined organics were washed with brine, dried

over MgSO₄, filtered and concentrated. Purified crude product on SiO₂ eluting with a gradient of EtOAc in hexanes to give 458 mg of the title compound. MS (*m/z*) 319 [M+H]⁺.

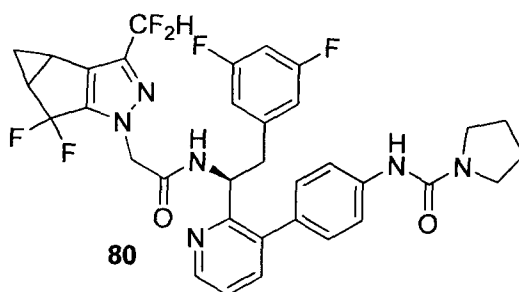
Synthesis of 2-(4-oxo-3-(trifluoromethyl)-4,5,6,7-tetrahydro-1H-indazol-1-yl)acetic acid (**79E**):

- 5 Prepared 508 mg of the title compound using a method analogous to **83E** using **79D**. MS (*m/z*) 263 [M+H]⁺.

Synthesis of (S)-5-(2-(2-(3,5-difluorophenyl)-1-(2-(4-oxo-3-(trifluoromethyl)-4,5,6,7-tetrahydro-1H-indazol-1-yl)acetamido)ethyl)pyridin-3-yl)-2-fluorobenzamide (**79F**):

- 10 Prepared 9.1 mg of the title compound by a method analogous to **54F** using **54B** and **79E**. MS (*m/z*) 616 [M+H]⁺.

Example 80

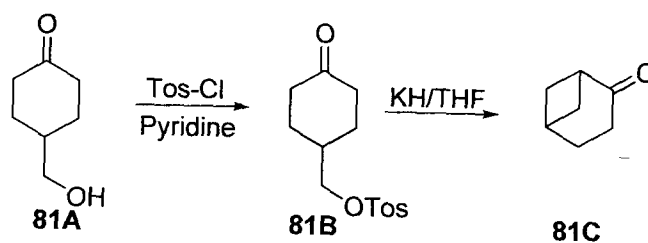


15

Synthesis of (S)-N-(1-(3-(4-(pyrrolidinylcarbonylamino)phenyl)-pyridin-2-yl)-2-(3,5-difluorophenyl)ethyl)-2-(3-(difluoromethyl)-5,6-dihydro-4,5-(methano)-6,6-difluorocyclopenta[c]pyrazol-1(4H)-yl)acetamide (**80**):

- Prepared 9.3 mg of the title compound by a method analogous to **68B** using **68A** and 4-(pyrrolidinylcarbonylamino)phenylboronic acid, pinacol ester. MS (*m/z*) 655 [M+H]⁺.
- 20

Example 81



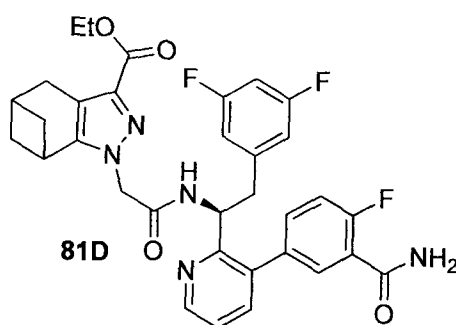
- 25 Synthesis of (4-oxocyclohexyl)methyl 4-methylbenzenesulfonate (**81B**):

To a 0 °C solution of Compound 81A (10 g, 78 mmol) in pyridine (78 ml) was added 4-toluenesulfonyl chloride (16.7 g, 87.8 mmol) in portions of 5 min. The reaction was stirred at 16 hrs at room temperature. The reaction was poured into 400 ml of a 1:1 mixture of Et₂O /H₂O. The layers were separated and the organic layer was extracted 2x with Et₂O. The combined organics were washed with H₂O (5x) and brine (2x). The organics were dried over MgSO₄, filtered and concentrated. Purified the crude product on SiO₂ eluting with a gradient of EtOAc in hexanes to give 18.5 g of the title compound after drying under reduced pressure. MS (*m/z*) 283 [M+H]⁺.

10 Synthesis of bicyclo[3.1.1]heptan-2-one (**81C**):

Potassium hydride (30% oil dispersion, 9.49 g, 71 mmol) was washed 3x with pentane and the dried under a stream of N₂. The solid was then suspended in THF (259 ml). Compound **81B** (10g, 35.5 mmol) was dissolved in THF (43 ml) and the resulting solution was added to the potassium hydride suspension over 5 min. The resulting mixture was heated at 50 °C for 16 hrs.

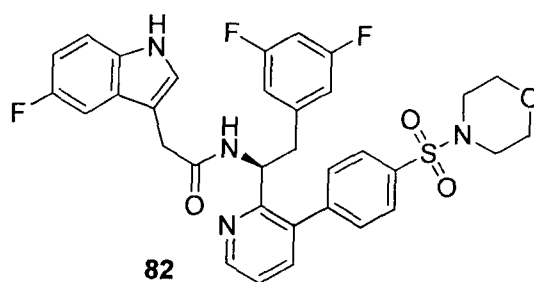
15 The cooled reaction mixture was filtered through a sintered glass funnel to remove gelatinous precipitate. The filtrate was concentrated to a small volume (150 ml) and poured into an ice water/ether mixture. The layers were separated and the aqueous layer was extracted 3x with Et₂O. The combined organics were washed with H₂O (3x), brine (1x), dried over MgSO₄, filtered and concentrated to a small volume. The crude material was used without further
20 purification (assumed 40% yield).



Synthesis of (S)-5-(2-(2-(3,5-difluorophenyl)-1-(2-(4,5,6,7-tetrahydro-3-carboethoxy-5,7-(methano)indazol-1-yl)acetamido)ethyl)pyridin-3-yl)-2-fluorobenzamide (**81D**):

25 Prepared 2.01g of the title compound by method analogous to Compound 90 starting with compound **81C**. MS (*m/z*) 618 [M+H]⁺.

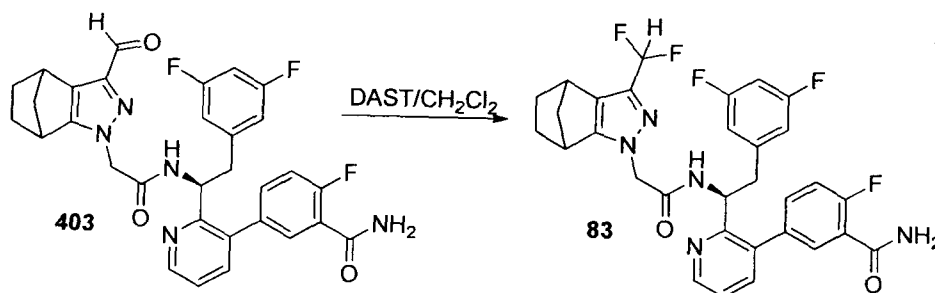
Example 82



Synthesis of (S)-N-(2-(3,5-difluorophenyl)-1-(3-(4-(morpholinosulfonyl)phenyl)pyridin-2-yl)ethyl)-2-(5-fluoro-1H-indol-3-yl)acetamide (**82**):

- 5 Prepared 25.2 mg of the title compound by a method analogous to **55F** using 4-(morpholinosulfonyl)phenyl boronic acid and **55E**. MS (m/z) 635 $[M+H]^+$.

Example 83



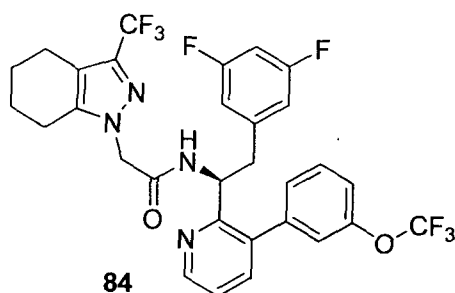
10

Synthesis of (S)-5-(2-(2-(3,5-difluorophenyl)-1-(2-(4,5,6,7-tetrahydro-3-difluoromethyl-4,7-(methano)indazol-1-yl)acetamido)ethyl)pyridin-3-yl)-2-fluorobenzamide (**83**):

- The crude Compound **403** (100 mg, 0.174 mmol) was dissolved in CH_2Cl_2 (2 ml). The resulting solution was treated with diethylaminosulfur trifluoride (DAST) (49 μl , 0.376 mmol) at room temperature for 5 hrs. The reaction mixture was poured into sat. aqueous NaHCO_3 . The layers were separated and the organic layer was washed 2x H_2O and 1x brine. The organics were dried over MgSO_4 , filtered and concentrated. The residue was purified by RP HPLC using a C18 column with a gradient of 0.1% H_2O , 0.1% TFA-acetonitrile to give 13.7 mg of the title compound. MS (m/z) 596 $[M+H]^+$.

20

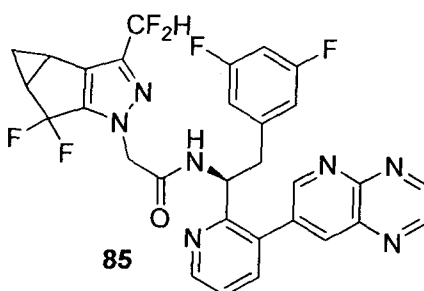
Example 84



Synthesis of (S)-N-(2-(3,5-difluorophenyl)-1-(3-(3-(trifluoromethoxy)phenyl)pyridin-2-yl)ethyl)-2-(3-(trifluoromethyl)-4,5,6,7-tetrahydro-1H-indazol-1-yl)acetamide (**84**):

Prepared 28.1 mg of the title compound by a method analogous to compound **57B** using **57A** and 3-trifluoromethoxyphenyl boronic acid. MS (m/z) 625 $[M+H]^+$.

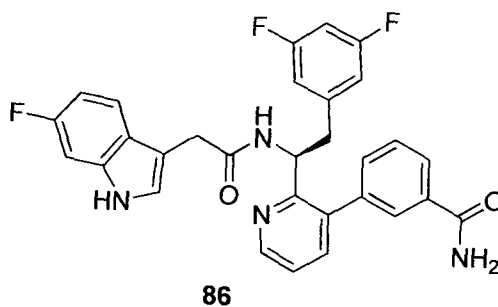
Example 85



Synthesis of (S)-N-(1-(3-(pyrido[2,3-b]pyrazin-7-yl)-pyridin-2-yl)-2-(3,5-difluorophenyl)ethyl)-2-(3-(difluoromethyl)-5,6-dihydro-4,5-(methano)-6,6-difluoro-cyclopenta[c]pyrazol-1(4H)-yl)acetamide (**85**):

Prepared 2.5 mg of the title compound by a method analogous to **68B** using **68A** and pyrido[2,3-b]pyrazin-7-ylboronic acid, pinacol ester. MS (m/z) 610 $[M+H]^+$.

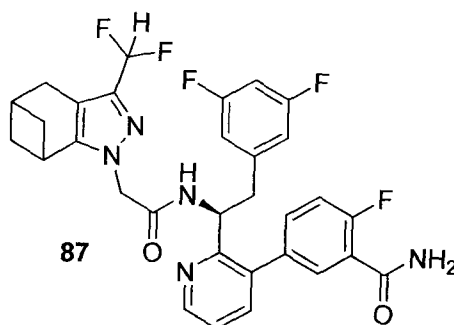
Example 86



Synthesis of (S)-3-(2-(2-(3,5-difluorophenyl)-1-(2-(6-fluoro-1H-indol-3-yl)acetamido)ethyl)pyridin-3-yl)benzamide (**86**):

Prepared 49 mg of the title compound by a method analogous to **50D** using 6-fluoro-3-indole acetic acid. ^1H NMR (400 MHz, $\text{d}_6\text{-DMSO}$) δ 10.82 (s, 1H), 8.66 (dd, 2H), 7.92 (d, 1H), 7.86 (s, 1H), 7.75 (s, 1H), 7.61 (dd, 1H), 7.49 – 7.35 (m, 4H), 7.26 (dd, 1H), 7.05 – 6.98 (m, 2H), 6.91 (t, 1H), 6.74 – 6.61 (m, 1H), 6.49 (d, 2H), 5.17 (dd, 3H), 4.70 – 4.65 (m, 1H), 3.44 (q, 2H), 2.95 (d, 2H). MS (m/z) 529 $[\text{M}+\text{H}]^+$.

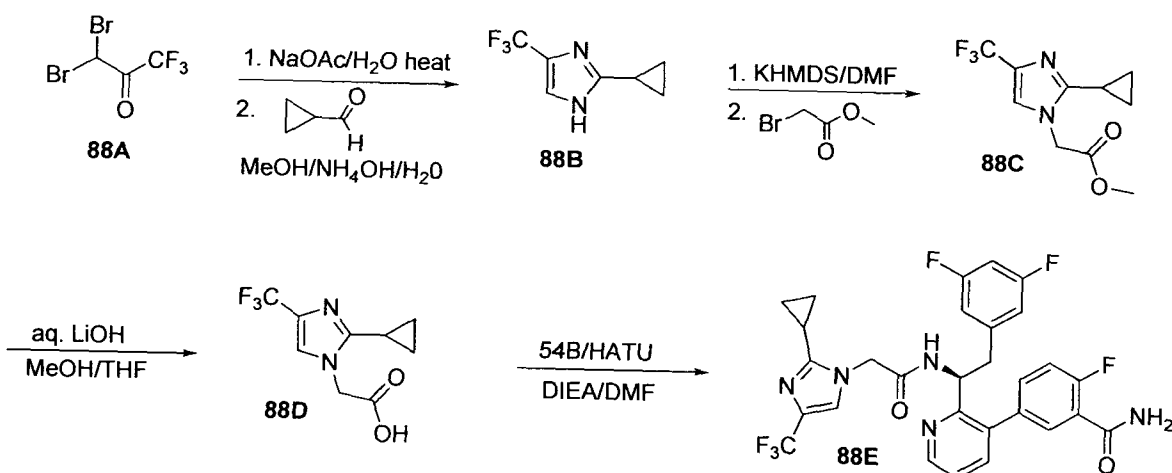
Example 87



Synthesis of (S)-5-(2-(2-(3,5-difluorophenyl)-1-(2-(4,5,6,7-tetrahydro-3-difluoromethyl-5,7-(methano)indazol-1-yl)acetamido)ethyl)pyridin-3-yl)-2-fluorobenzamide (**87**):

Prepared 41.6 mg of the title compound by method analogous to compound **83** starting with compound **96**. MS (m/z) 596 $[\text{M}+\text{H}]^+$.

Example 88



Synthesis of 2-cyclopropyl-4-(trifluoromethyl)-1H-imidazole (**88B**):

To a suspension of 3,3-dibromo-1-(trifluoromethyl)propane (2.0 g, 7.41 mmol) in H_2O (10 ml) was added sodium acetate (1.33 g, 16.2 mmol). The mixture was heated at 100°C for 30 min. and then cooled to room temperature. A solution of cyclopropylcarboxaldehyde (646 μl , 8.64 mmol) in MeOH (4 ml) was added to the reaction mixture followed by NH_4OH (2.8 ml, 20%

in H₂O). The reaction was stirred at room temperature overnight. The mixture was extracted 3x with EtOAc. The combined organics were washed with brine, dried over MgSO₄, filtered and concentrated to give 1.07 g of crude title product which was used directly for the next step.

- 5 Synthesis of methyl-2-(2-cyclopentyl-4-(trifluoromethyl)-1H-imidazol-1-yl)acetate (**88C**):
The crude product **88B** was dissolved in DMF (60 ml). Solid KHMDS (1.45 g, 7.29 mmol) was added and the reaction was stirred 5 min. at room temperature. Added methyl bromoacetate (690 ul, 7.29 mmol) and then stirred the reaction for 1 hr at room temperature. The mixture was concentrated under reduced pressure to a small volume then partitioned between EtOAc and
10 H₂O. Extracted the aqueous layer 2x EtOAc. The combined organics were washed with brine, dried over MgSO₄, filtered and concentrated. The crude product was purified by column chromatography on SiO₂ to give 630 mg of the title compound.

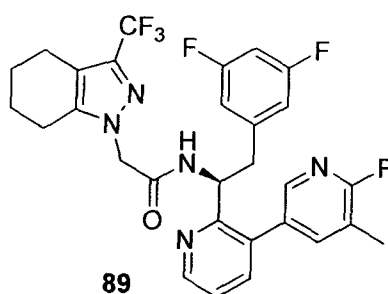
Synthesis of 2-(2-cyclopentyl-4-(trifluoromethyl)-1H-imidazol-1-yl) acetic acid (**88D**):

- 15 Prepared 83 mg of the title compound by a method analogous to **74C** using **88C**.

Synthesis of (S)-5-(2-(1-(2-(2-cyclopropyl-4-(trifluoromethyl)-1H-imidazol-1-yl)acetamido)-2-(3,5-difluorophenyl)ethyl)pyridin-3-yl)-2-fluorobenzamide (**88E**):

- Prepared 29.4 mg of the title compound by a method analogous to **54G** using **88D** and **54B**. MS
20 (*m/z*) 588 [M+H]⁺.

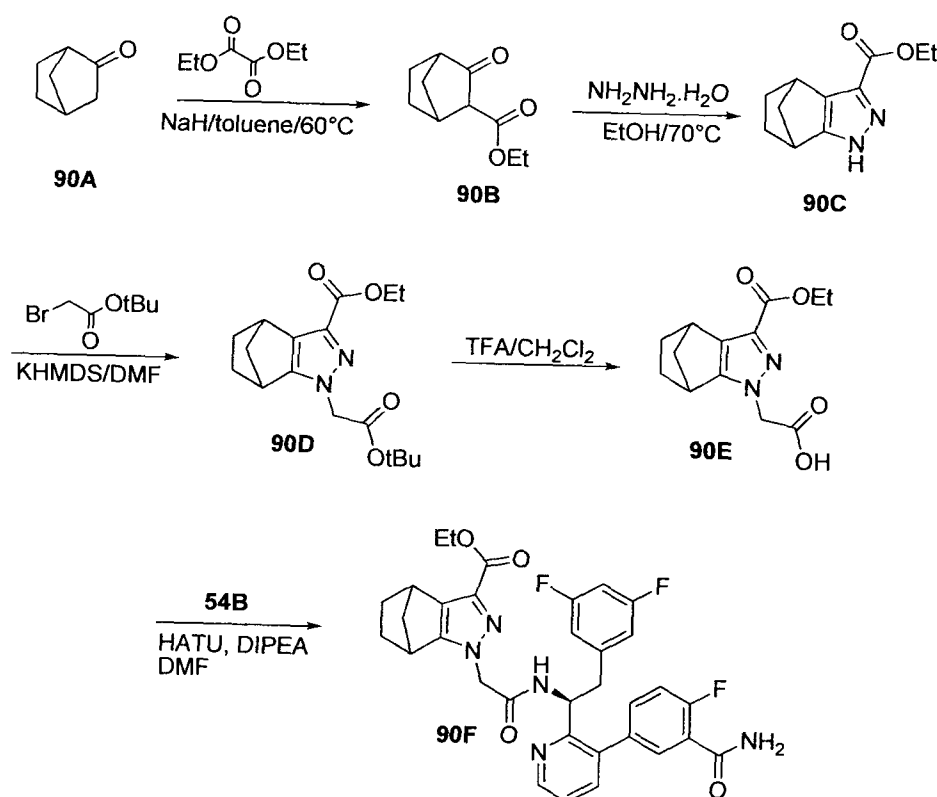
Example 89



- 25 Synthesis of (S)-N-(2-(3,5-difluorophenyl)-1-(6'-fluoro-5'-methyl-3,3'-bipyridin-2-yl)ethyl)-2-(3-(trifluoromethyl)-4,5,6,7-tetrahydro-1H-indazol-1-yl)acetamide (**89**):

Prepared 28.2 mg of the title compound by a method analogous to compound **57B** using **57A** and 6-fluoro-5-methylpyridin-3-ylboronic acid. MS (*m/z*) 574 [M+H]⁺.

Example 90



Synthesis of ethyl 3-oxobicyclo[2.2.1]heptane-2-carboxylate (**90B**):

Suspended NaH (400 mg, 10 mmol) in toluene (8 ml). Added diethyl oxalate (1.26 ml, 9.2 mmol) and heated mixture to 60 °C. Added a solution of norbornanone (850 mg, 7.7 mmol) in toluene (4 ml). Stirred reaction mixture for 1 hr. Cooled reaction to room temperature and the poured into ice. Neutralized aqueous layer to pH=2 with 1N aq. HCl. Extracted mixture 3x with EtOAc. The combined organics were washed with brine, dried over MgSO₄, filtered and concentrated. Purified residue on SiO₂ column using a gradient of EtOAc and hexanes to give 1.33 g of the title compound.

Synthesis of 4,5,6,7-tetrahydro-3-carboethoxy-4,7-(methano)indazole (**90C**):

Dissolved **90B** (1.33 g, 6.33 mmol) in EtOH (13 ml). Added hydrazine hydrate (405 ul, 6.33 mmol) and heated reaction to 70 °C. Stirred reaction for 72 hrs at 70 °C. Cooled reaction to room temperature, then partition mixture between EtOAc and H₂O. Extracted aqueous layer 1x EtOAc. Dried combined organic over MgSO₄, filtered and concentrated. Purified the residue on SiO₂ column using a gradient of EtOAc and hexanes to give 497 mg of the title compound. MS (*m/z*) 206 [M+H]⁺.

Synthesis of t-butyl 2-(4,5,6,7-tetrahydro-3-carboethoxy-4,7-(methano)indazol-1-yl)acetate (**90D**):

Prepared 542 mg of the title compound by a method analogous to **107C** using **90C**. MS (*m/z*) 321 [M+H]⁺.

5

Synthesis of 2-(4,5,6,7-tetrahydro-3-carboethoxy-4,7-(methano)indazol-1-yl)acetic acid (**90E**):

Prepared 455 mg of the title compound by a method analogous to **107D** using **90D**. MS (*m/z*) 265 [M+H]⁺.

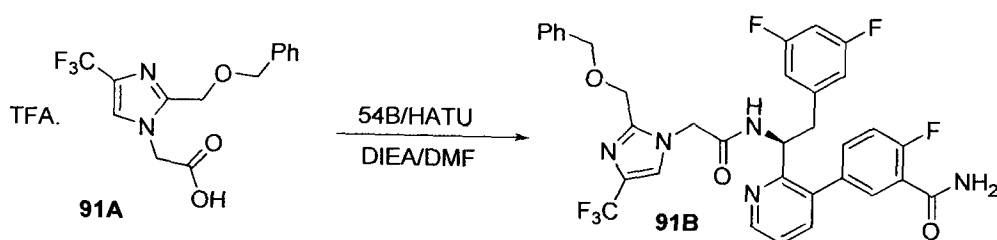
10 Synthesis of (S)-5-(2-(2-(3,5-difluorophenyl)-1-(2-(4,5,6,7-tetrahydro-3-carboethoxy-4,7-(methano)indazol-1-yl)acetamido)ethyl)pyridin-3-yl)-2-fluorobenzamide (**90F**):

Prepared 236 mg of the title compound using a method analogous to **107E** using **90E** and **54B**.

¹H NMR (400 MHz, CD₃OD) δ 8.69 (s, 1H), 7.65 (t, 1H), 7.44 (s, 2H), 7.31 (s, 1H), 7.26 – 7.17 (m, 1H), 6.66 (d, 1H), 6.35 (d, 2H), 5.35 (d, 1H), 4.30 (q, 2H), 3.50 (s, 1H), 3.05 (d, 2H), 1.87 (d, 4H), 1.66 (s, 1H), 1.34 (t, 3H), 1.09 (s, 2H). MS (*m/z*) 618 [M+H]⁺.

15

Example 91



Synthesis of 2-(2-(benzyloxymethyl)-4-(trifluoromethyl)-1H-imidazol-1-yl)acetic acid (**91A**):

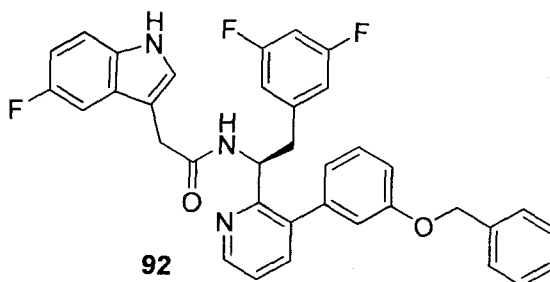
20 Prepared 115 mg of the title compound by a method analogous to **107D** using benzyloxyacetaldehyde.

Synthesis of (S)-5-(2-(1-(2-(2-(benzyloxymethyl)-4-(trifluoromethyl)-1H-imidazol-1-yl)acetamido)-2-(3,5-difluorophenyl)ethyl)pyridin-3-yl)-2-fluorobenzamide (**91B**):

25 Prepared 81.2 mg of the title compound by a method analogous to **107E** using **107D** and **54B**.

¹H NMR (400 MHz, CD₃OD) δ 8.69 (s, 1H), 7.57 (d, 2H), 7.39 (s, 2H), 7.22 (d, 6H), 6.64 (s, 1H), 6.24 (s, 2H), 5.28 (s, 1H), 4.54 (d, 2H), 4.40 (s, 2H), 2.95 (d, 2H). MS (*m/z*) 668 [M+H]⁺.

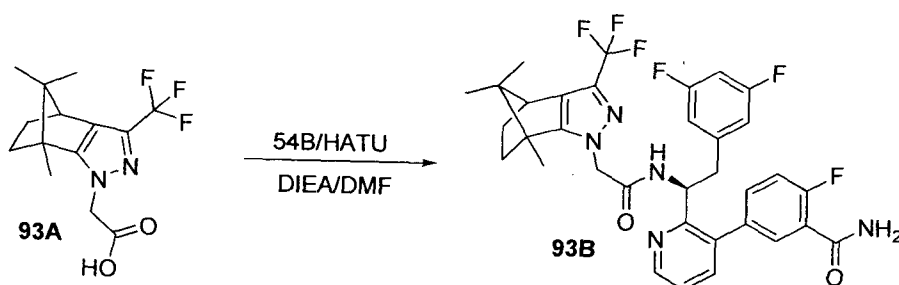
Example 92



Synthesis of (S)-N-(1-(3-(3-(benzyloxy)phenyl)pyridin-2-yl)-2-(3,5-difluorophenyl)ethyl)-2-(5-fluoro-1H-indol-3-yl)acetamide (**92**):

- 5 Prepared 25 mg of the title compound by a method analogous to **55F** using 3-phenoxyphenylboronic acid and **55E**. MS (m/z) 592 $[M+H]^+$.

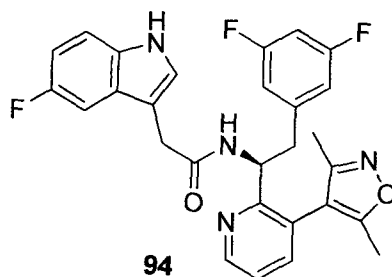
Example 93



Synthesis of (S)-5-(2-(2-(3,5-difluorophenyl)-1-(2-(D-4,5,6,7-Tetrahydro-3-trifluoromethyl-7,8,8-trimethyl-1H-4,7-(methano)indazol-1-yl)acetamido)ethyl)pyridin-3-yl)-2-fluorobenzamide (**93B**):

- 15 Prepared 60.9 mg of the title compound by a method analogous to **74D** using **93A**, obtained by a method analogous to **74C**, and **54B**. ^1H NMR (400 MHz, CD_3OD) δ 8.69 (dd, 1H), 7.66 (dd, 1H), 7.46 (dd, 2H), 7.28 (s, 1H), 7.24 – 7.18 (m, 1H), 6.68 (t, 1H), 6.36 (d, 2H), 5.37 (t, 1H), 3.06 (d, 2H), 2.84 (d, 1H), 2.06 (d, 1H), 1.76 (t, 1H), 1.24 (d, 1H), 1.16 (s, 3H), 1.07 – 0.94 (m, 1H), 0.90 (s, 3H), 0.73 (s, 3H). MS (m/z) 656 $[M+H]^+$.

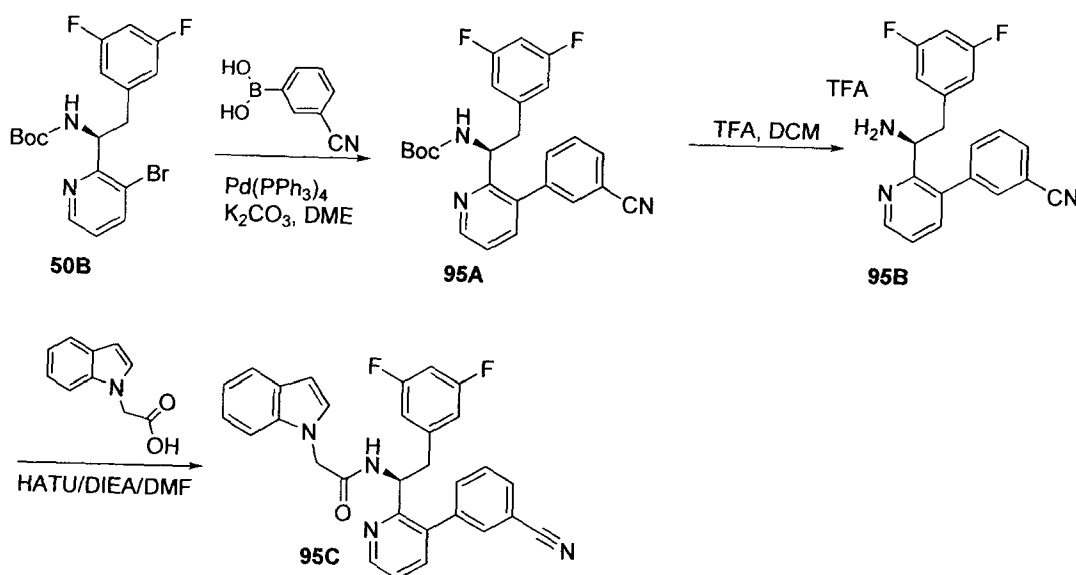
Example 94



Synthesis of N-((1S)-2-(3,5-difluorophenyl)-1-(3-(3,5-dimethylisoxazol-4-yl)pyridin-2-yl)ethyl)-2-(5-fluoro-1H-indol-3-yl)acetamide (**94**):

- 5 Prepared 2 mg of the title compound by a method analogous to **55F** using 3,5-dimethyl-1,2-oxazolyl-4-boronic acid and **55E**. MS (m/z) 505 $[M+H]^+$.

Example 95



- 10 Synthesis of (S)-tert-butyl 1-(3-(3-cyanophenyl)pyridin-2-yl)-2-(3,5-difluorophenyl)ethylcarbamate (**95A**):

Prepared 60 mg of the title compound by a method analogous to **54A** using 3-cyanophenyl boronic acid.

- 15 Synthesis of (S)-3-(2-(1-amino-2-(3,5-difluorophenyl)ethyl)pyridin-3-yl)benzonitrile trifluoroacetate (**95B**)

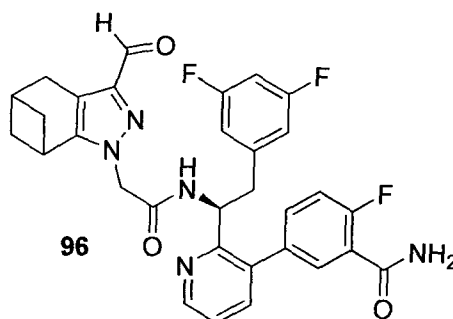
Prepared 61.9 mg of the title compound by a method analogous to **54B**.

Synthesis of (S)-N-(1-(3-(3-cyanophenyl)pyridin-2-yl)-2-(3,5-difluorophenyl)ethyl)-2-(1H-indol-1-yl)acetamide (**95C**):

Prepared 33 mg of the title compound by a method analogous to **74D** using compound **95B** and indole-1-acetic acid. MS (m/z) 493 $[M+H]^+$.

5

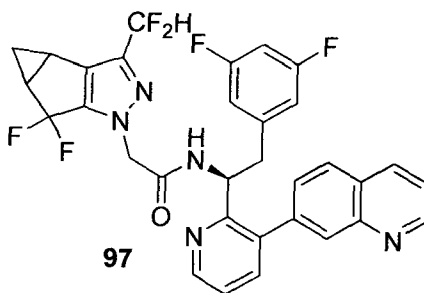
Example 96



Synthesis of (S)-5-(2-(2-(3,5-difluorophenyl)-1-(2-(4,5,6,7-tetrahydro-3-formyl-5,7-(methano)indazol-1-yl)acetamido)ethyl)pyridin-3-yl)-2-fluorobenzamide (**96**):

10 Prepared 256 mg of the title compound by a method analogous to compound **403** starting with compound **81D**. MS (m/z) 574 $[M+H]^+$.

Example 97

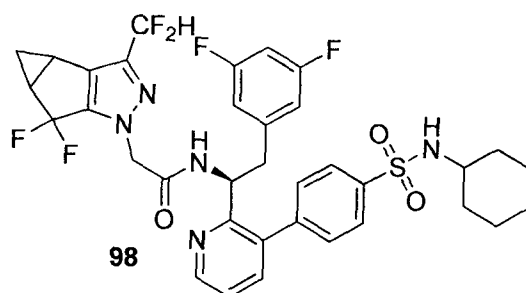


15 Synthesis of (S)-N-(1-(3-(quinoline-7-yl)-pyridin-2-yl)-2-(3,5-difluorophenyl)ethyl)-2-(3-(difluoromethyl)-5,6-dihydro-4,5-(methano)-6,6-difluoro-cyclopenta[c]pyrazol-1(4H)-yl)acetamide (**97**):

Prepared 6.1 mg of the title compound by a method analogous to **68B** using **68A** and quinolin-7-yl-7-boronic acid. MS (m/z) 608 $[M+H]^+$.

20

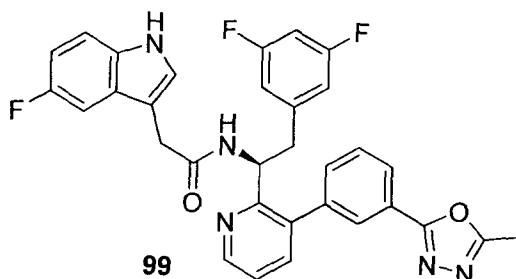
Example 98



Synthesis of (S)-N-(1-(3-(4-(N-cyclohexylsulfamoyl)phenyl)-pyridin-2-yl)-2-(3,5-difluorophenyl)ethyl)-2-(3-(difluoromethyl)-5,6-dihydro-4,5-(methano)-6,6-difluorocyclopenta[c]pyrazol-1(4H)-yl)acetamide (**98**):

- 5 Prepared 17.3 mg of the title compound by a method analogous to **68B** using **68A** and 4-(N-cyclohexylsulfamoyl)phenylboronic acid. MS (m/z) 718 $[M+H]^+$.

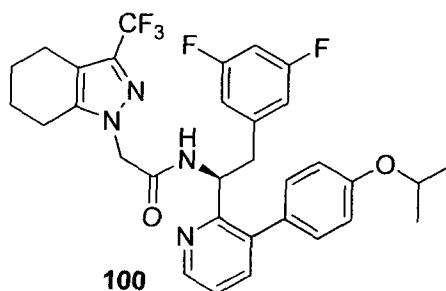
Example 99



10 Synthesis of (S)-N-(2-(3,5-difluorophenyl)-1-(3-(3-(5-methyl-1,3,4-oxadiazol-2-yl)phenyl)pyridin-2-yl)ethyl)-2-(5-fluoro-1H-indol-3-yl)acetamide (**99**):

Prepared 9.5 mg of the title compound by a method analogous to **55F** using 3-(5-methyl-1,3,4-oxadiazol-2-yl)phenylboronic acid and **55E**. MS (m/z) 569 $[M+H]^+$.

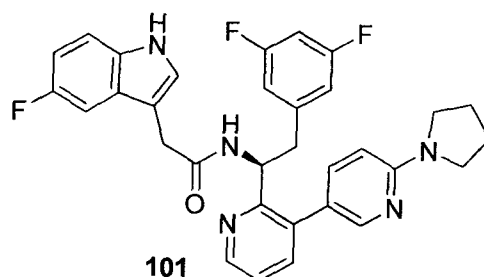
Example 100



Synthesis of (S)-N-(2-(3,5-difluorophenyl)-1-(3-(4-isopropoxyphenyl)pyridin-2-yl)ethyl)-2-(3-(trifluoromethyl)-4,5,6,7-tetrahydro-1H-indazol-1-yl)acetamide (**100**):

Prepared 4.7 mg of the title compound by a method analogous to compound **57B** using **57A** and 4-isopropoxyphenyl boronic acid. MS (m/z) 599 $[M+H]^+$.

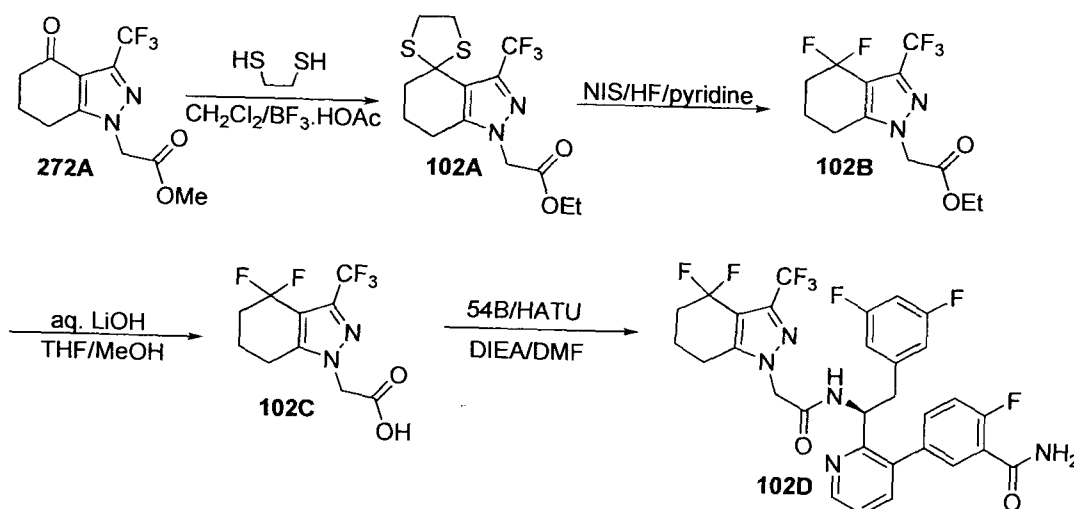
Example 101



Synthesis of (S)-N-(2-(3,5-difluorophenyl)-1-(6'-(pyrrolidin-1-yl)-3,3'-bipyridin-2-yl)ethyl)-2-(5-fluoro-1H-indol-3-yl)acetamide (**101**):

Prepared 35.5 mg of the title compound by a method analogous to **55F** using 6-(pyrrolidin-1-yl)pyridin-3-ylboronic acid and **55E**. MS (m/z) 566 $[M+H]^+$.

Example 102



Synthesis of ethyl 2-(3'-(trifluoromethyl)-6',7'-dihydrospiro[[1,3]dithiolane-2,4'-indazole]-1'(5'H)-yl)acetate (**102A**):

To a solution of **272A** (290 mg, 1.0 mmol) in CH_2Cl_2 was added 1,2-ethanedithiol (126 μl , 1.5 mmol) and $\text{BF}_3 \cdot 2\text{HOAc}$ (210 μl , 1.5 mmol). The reaction mixture was stirred at room temperature for 16 hrs then partitioned between CH_2Cl_2 and water. Extracted the aqueous layer 1x CH_2Cl_2 . Washed the combined organics 1x with sat. aq. NaHCO_3 , H_2O and brine. Dried the organics over MgSO_4 , filtered and concentrated. Purified the crude product on SiO_2 eluting with a gradient of EtOAc in hexanes to give 334 mg of the title compound.

Synthesis of ethyl 2-(4,4-difluoro-3-(trifluoromethyl)-4,5,6,7-tetrahydro-1H-indazol-1-yl)acetate (**102B**):

A solution of N-iodosuccinimide (423 mg, 1.88 mmol) and HF/pyridine (2.6 ml) in CH₂Cl₂ (2.6 ml) in a Teflon reaction vessel was cooled to -70 °C under N₂. A solution of Compound **102A** (334 mg, 0.91 mmol) in CH₂Cl₂ (2.6 ml) was added to the cooled reaction mixture over 5 min. The resulting mixture was stirred at -70 °C for 45min. then warmed to -50 °C for 20min. The reaction vessel was placed in an ice bath and the reaction was quenched with sat. aq. NaHCO₃. The mixture was diluted with CH₂Cl₂ and the layers were separated. Extracted the aqueous layer 2x CH₂Cl₂. Washed the combined organics 1x with brine. Dried the organics over MgSO₄, filtered and concentrated. Purified the crude product on SiO₂ eluting with a gradient of EtOAc in hexanes to give 112 mg of the title compound.

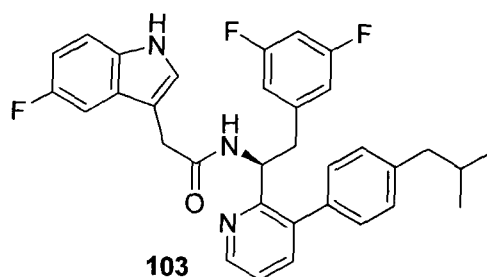
Synthesis of Ethyl 2-(4,4-difluoro-3-(trifluoromethyl)-4,5,6,7-tetrahydro-1H-indazol-1-yl)acetate (**102C**):

Prepared 79.2 mg of the title compound by a method analogous to compound **401B** using compound **102B**.

Synthesis of (S)-5-(2-(1-(2-(4,4-difluoro-3-(trifluoromethyl)-4,5,6,7-tetrahydro-1H-indazol-1-yl)acetamido)-2-(3,5-difluorophenyl)ethyl)pyridin-3-yl)-2-fluorobenzamide (**102D**):

Prepared 130 mg of the title compound by a method analogous to **54F** using **102C** and **54B**. ¹H NMR (400 MHz, CD₃OD) δ 8.70 (dd, 1H), 7.65 (d, 1H), 7.45 (dd, 2H), 7.33 (s, 1H), 7.22 (dd, 1H), 6.67 (t, 1H), 6.34 (d, 2H), 5.36 (t, 1H), 4.86 (d, 2H), 3.07 (d, 2H), 2.57 (d, 2H), 2.17 (d, 2H), 2.00 (d, 2H). MS (*m/z*) 638 [M+H]⁺.

Example 103

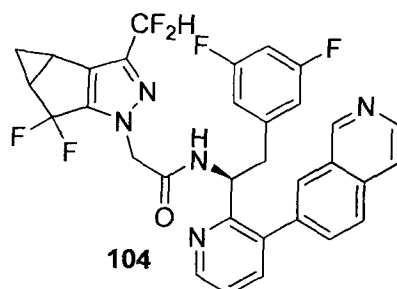


Synthesis of (S)-N-(2-(3,5-difluorophenyl)-1-(3-(4-isobutylphenyl)pyridin-2-yl)ethyl)-2-(5-fluoro-1H-indol-3-yl)acetamide (**103**):

Prepared 37 mg of the title compound by a method analogous to **55F** using 4-isobutylphenylboronic acid and **55E**. MS (m/z) 542 $[M+H]^+$.

Example 104

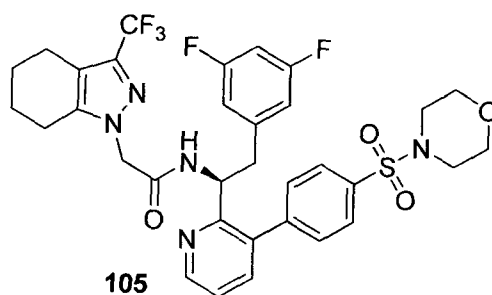
5



Synthesis of (S)-N-(1-(3-(isoquinolin-7-yl)pyridin-2-yl)-2-(3,5-difluorophenyl)ethyl)-2-(3-(difluoromethyl)-5,6-dihydro-4,5-(methano)-6,6-difluoro-cyclopenta[c]pyrazol-1(4H)-yl)acetamide (**104**):

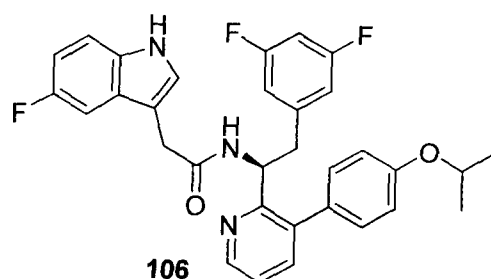
- 10 Prepared 11.7 mg of the title compound by a method analogous to **68B** using **68A** and isoquinolin-7-ylboronic acid. MS (m/z) 608 $[M+H]^+$.

Example 105



- 15 Synthesis of (S)-N-(2-(3,5-difluorophenyl)-1-(3-(4-(morpholinosulfonyl)phenyl)pyridin-2-yl)ethyl)-2-(3-(trifluoromethyl)-4,5,6,7-tetrahydro-1H-indazol-1-yl)acetamide (**105**):
Prepared 38.6 mg of the title compound by a method analogous to compound **57B** using **57A** and 4-(morpholinosulfonyl)phenylboronic acid. MS (m/z) 690 $[M+H]^+$.

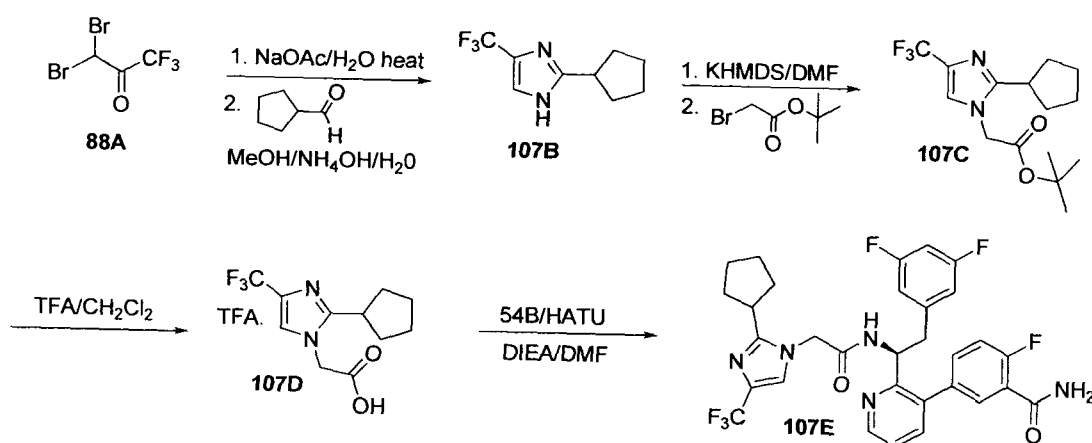
20 Example 106



Synthesis of (S)-N-(2-(3,5-difluorophenyl)-1-(3-(4-isopropoxyphenyl)pyridin-2-yl)ethyl)-2-(5-fluoro-1H-indol-3-yl)acetamide (**106**):

- 5 Prepared 25.4 mg of the title compound by a method analogous to **55F** using 4-isopropoxyphenylboronic acid and **55E**. MS (m/z) 544 $[M+H]^+$.

Example 107



- 10 Synthesis of 2-cyclopentyl-4-(trifluoromethyl)-1H-imidazole (**107B**):

To a suspension of 3,3-dibromo-1-trifluoromethyl-propane (2.35 g, 8.72 mmol) in H₂O was added sodium acetate (1.67 g, 20.4 mmol). The mixture was heated at 100 °C for 30 min. and then cooled to room temperature. A solution of cyclopentanecarboxaldehyde (1 g, 10.2 mmol) in 4.8 ml of MeOH was added to the reaction mixture followed by NH₄OH (4.8 ml, 20% in H₂O). The reaction was stirred at room temperature overnight. The mixture was extracted 3x with EtOAc. The combined organics were washed with brine, dried over MgSO₄, filtered and concentrated. The crude product was used directly for the next step.

Synthesis of tert-butyl 2-(2-cyclopentyl-4-(trifluoromethyl)-1H-imidazol-1-yl)acetate (**107C**):

- 20 The crude product from **107B** (8.72 mmol) was dissolved in 86 ml DMF. Solid KHMDS (2.09 g, 10.5 mmol) was added and the reaction was stirred 5 min. at room temperature. Added t-butyl bromoacetate (1.52 ml, 10.5 mmol) and then stirred the reaction for 30 min. at room

temperature. The mixture was concentrated under reduced pressure to a small volume then partitioned between EtOAc and H₂O. Extracted the aqueous layer 2x EtOAc. The combined organics were washed with brine, dried over MgSO₄, filtered and concentrated. The crude product was purified by column chromatography on SiO₂ to give 279 mg of the title compound.

5

Synthesis of 2-(2-cyclopentyl-4-(trifluoromethyl)-1H-imidazol-1-yl)acetic acid (**107D**):

Dissolved **107C** (84 mg, 0.264 mmol) in 1:1 TFA/CH₂Cl₂ (2 ml). Added 2 drops of H₂O and stirred reaction at room temperature for 4 hrs. The reaction mixture was concentrated *in vacuo*.

The residue was azeotroped 2x with Et₂O and then dried under reduced pressure to give 105 mg of the title compound.

10

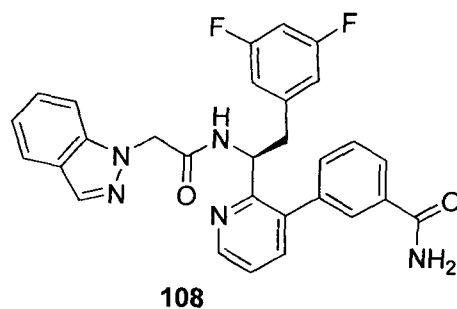
Synthesis of (S)-5-(2-(1-(2-(2-cyclopentyl-4-(trifluoromethyl)-1H-imidazol-1-yl)acetamido)-2-(3,5-difluorophenyl)ethyl)pyridin-3-yl)-2-fluorobenzamide (**107E**):

Prepared 58.5 mg of the title compound by a method analogous to **54G** using **107D** and **54B**. ¹H

15

NMR (400 MHz, CD₃OD) δ 8.62 (d, 1H), 7.51 (d, 1H), 7.39 (s, 2H), 7.32 (dd, 1H), 7.29 – 7.22 (m, 1H), 7.18 – 7.11 (m, 1H), 6.60 (s, 1H), 6.29 (d, 2H), 5.26 (t, 1H), 4.71 (d, 2H), 3.05 – 2.92 (m, 2H), 2.87 (s, 1H), 1.69 (s, 8H). MS (*m/z*) 616 [M+H]⁺.

Example 108



20

Synthesis of (S)-3-(2-(1-(2-(1H-indazol-1-yl)acetamido)-2-(3,5-difluorophenyl)ethyl)pyridin-3-yl)benzamide (**108**):

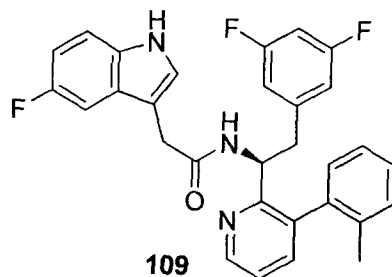
Prepared 22 mg of the title compound by a method analogous to **50C** using benzimidazole-1-

acetic acid. ¹H NMR (400 MHz, dmsO) δ 8.91 (d, 1H), 8.69 (dd, 1H), 7.96 (s, 1H), 7.96 – 7.81

25

(m, 2H), 7.75 – 7.59 (m, 3H), 7.53 – 7.36 (m, 3H), 7.27 (q, 2H), 7.07 (t, 1H), 6.93 (t, 1H), 6.51 (d, 2H), 5.18 (dd, 2H), 5.04 (s, 2H), 4.59 – 4.54 (m, 1H), 3.08 – 2.53 (m, 3H). MS (*m/z*) 512 [M+H]⁺.

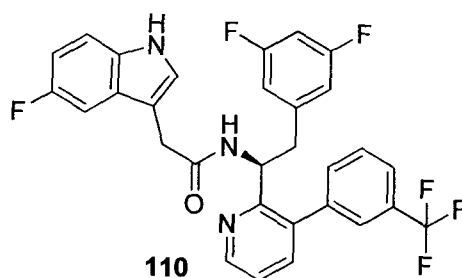
Example 109



Synthesis of (S)-N-(2-(3,5-difluorophenyl)-1-(3-(3-tolylpyridin-2-yl)ethyl)-2-(5-fluoro-1H-indol-3-yl)acetamide (**109**):

Prepared 16.7 mg of the title compound by a method analogous to **55F** using 2-methylphenylboronic acid and **55E**. MS (m/z) 500 $[M+H]^+$.

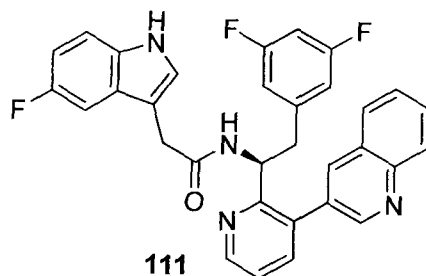
Example 110



Synthesis of (S)-N-(2-(3,5-difluorophenyl)-1-(3-(3-(trifluoromethyl)phenyl)pyridin-2-yl)ethyl)-2-(5-fluoro-1H-indol-3-yl)acetamide (**110**):

Prepared 34 mg of the title compound by a method analogous to **55F** using 3-trifluoromethylphenyl boronic acid and **55E**. MS (m/z) 554 $[M+H]^+$.

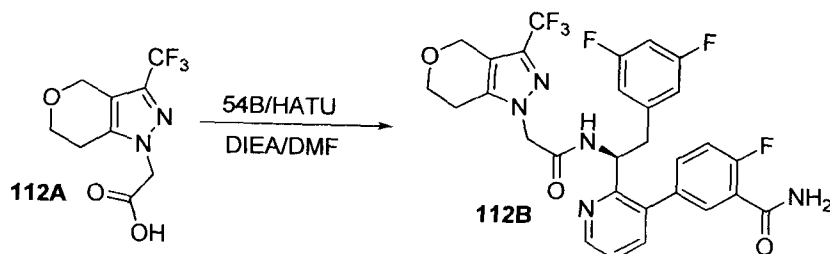
Example 111



Synthesis of (S)-N-(2-(3,5-difluorophenyl)-1-(3-(quinolin-3-yl)pyridin-2-yl)ethyl)-2-(5-fluoro-1H-indol-3-yl)acetamide (**111**):

Prepared 22.7 mg of the title compound by analogous method to **55F** using quinoline-3-ylboronic acid and **55E**. MS (m/z) 537 $[M+H]^+$.

Example 112



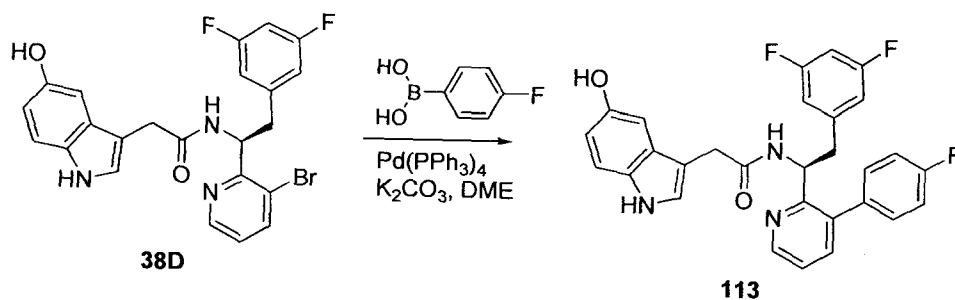
5

Synthesis of (S)-5-(2-(2-(3,5-difluorophenyl)-1-(2-(3-(trifluoromethyl)-6,7-dihydropyrano[4,3-c]pyrazol-1(4H)-yl)acetamido)ethyl)pyridin-3-yl)-2-fluorobenzamide (**112B**):

Prepared 58.5 mg of the title compound by a method analogous to **54G** using **112A** (prepared by analogous method to **107D**) and **54B**. ^1H NMR (400 MHz, CD_3OD) δ 8.62 (d, 1H), 7.56 (dd, 1H), 7.27 (ddd, 4H), 6.59 (t, 1H), 6.26 (d, 2H), 5.28 (t, 1H), 4.56 (s, 2H), 3.79 (t, 2H), 3.08 – 2.90 (m, 2H), 2.78 – 2.27 (m, 3H). MS (m/z) 605 $[M+H]^+$.

10

Example 113



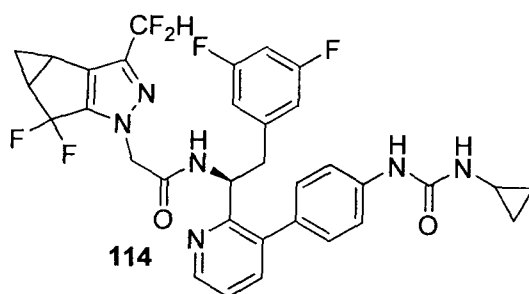
113

15 Synthesis of (S)-N-(2-(3,5-difluorophenyl)-1-(3-(4-fluorophenyl)pyridin-2-yl)ethyl)-2-(5-hydroxy-1H-indol-3-yl)acetamide (**113**):

To a solution of **38D** (50 mg, 0.103 mmol) and 4-fluorophenyl boronic acid (15.7 mg, 0.113 mmol) in 1 ml DME was added 0.4N aq. K_2CO_3 (515 μl) and $\text{Pd}(\text{PPh}_3)_4$ (11.9 mg, 0.0010 mmol). The resulting mixture was heated at 120 $^\circ\text{C}$ for 10 min. under microwave irradiation. Solvents were concentrated *in vacuo* and the residue was purified by RP HPLC using a C18 column with a gradient of 0.1% H_2O , 0.1% TFA-acetonitrile, to provide 31 mg of the title compound. ^1H NMR (400 MHz, dmsO) δ 10.47 (s, 1H), 8.62 (dd, 1H), 8.46 (d, 1H), 7.51 (dd, 1H), 7.34 (dd, 1H), 7.15 (dd, 4H), 7.05 (d, 1H), 6.91 (dd, 2H), 6.77 (d, 2H), 6.53 (dd, 1H), 6.34 (d, 2H), 5.15 (q, 2H), 4.27 – 4.22 (m, 1H), 3.39 (s, 2H), 2.90 (d, 2H). MS (m/z) 501 $[M+H]^+$.

20

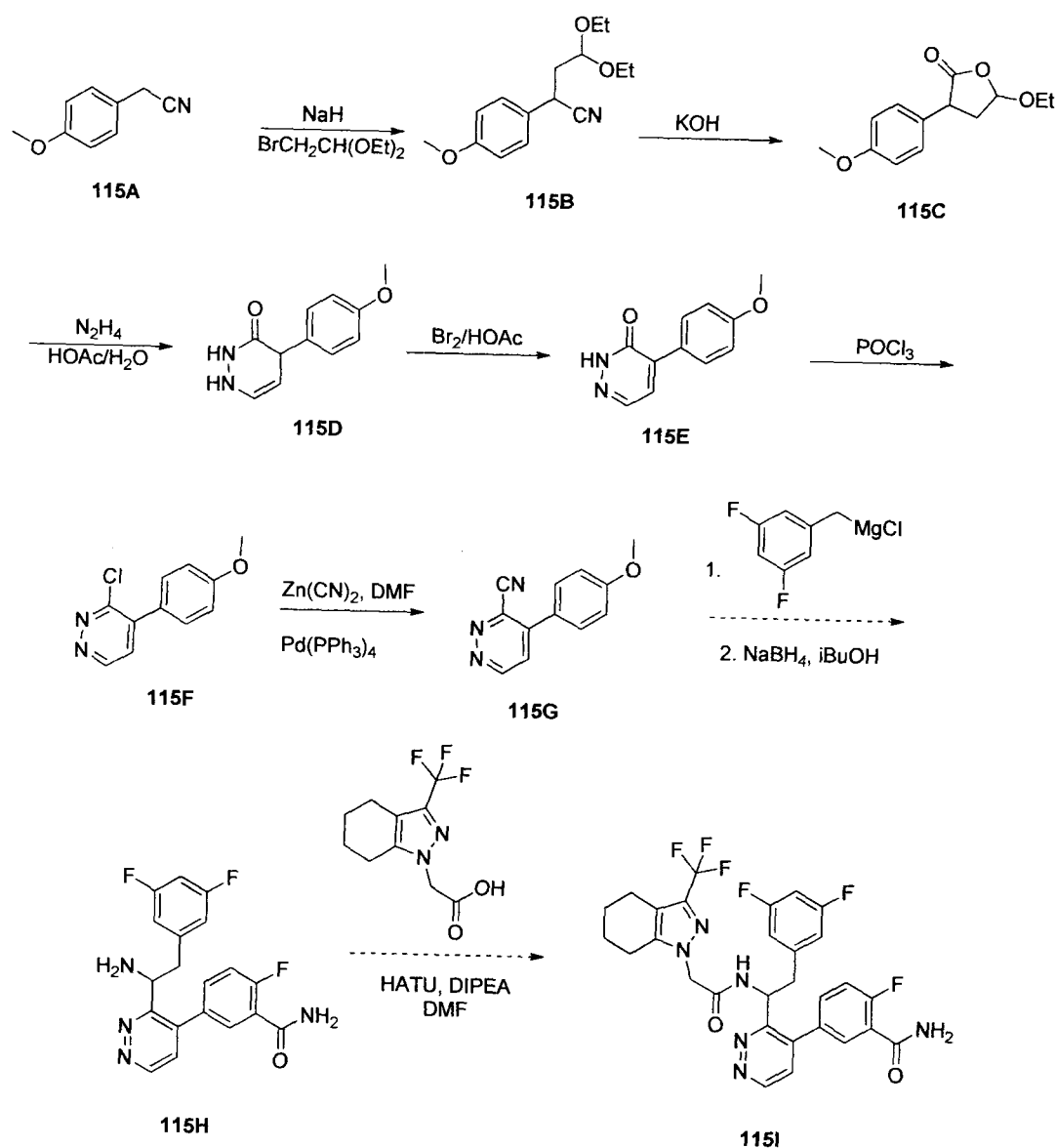
Example 114



5 Synthesis of (S)-N-(1-(3-(4-(3-cyclopropylureido)phenyl)-pyridin-2-yl)-2-(3,5-difluorophenyl)ethyl)-2-(3-(difluoromethyl)-5,6-dihydro-4,5-(methano)-6,6-difluoro-cyclopenta[c]pyrazol-1(4H)-yl)acetamide (**114**):

Prepared 12.2 mg of the title compound by a method analogous to **68B** using **68A** and 4-(3-cyclopropylureido)phenylboronic acid, pinacol ester. MS (m/z) 655 [$M+H$]⁺.

10 Example 115



Synthesis of 4,4-diethoxy-2-(4-methoxyphenyl)butanenitrile (**115B**):

Compound 115A (21.0 g, 143 mmol) was added to a suspension of NaH (8.9 g, 215 mmol) in THF (250 ml), and stirred at 50 °C for 1.5 hr. Ethyl bromoacetate (33.82 g, 172 mmol) was added to the mixture which was then boiled under reflux for 2 hr. The mixture was diluted with water, extracted with EtOAc (400 ml $\times$ 3) and washed with brine (1000 ml). The combined extracts are dried with anhydrous Na₂SO₄, filtered and concentrated. The residue was purified by column chromatography on silica gel to afford the title compound (29.2 g, 78% yield) as a pale yellow oil.

Synthesis of 5-ethoxy-3-(4-methoxyphenyl)dihydrofuran-2(3H)-one (**115C**):

Compound 115B (29.0 g, 110 mmol) and KOH (30.9 g, 550 mmol) are dissolved in EtOH (300

ml) and water (100 ml). The solution was boiled under reflux for 3 days, acidified with 10 N HCl and evaporated, extracted with EtOAc (400 ml 4) and washed with brine (1500 ml). The combined extracts are dried with anhydrous Na₂SO₄, filtered and concentrated. The residue was purified by column chromatography on silica gel (PE/EtOAc = 8/1) to afford the title compound (14.0 g, 54% yield) as a pale yellow oil.

Synthesis of 4-(4-methoxyphenyl)-1,2-dihydropyridazin-3(4H)-one (**115D**):

Compound 115C (3.54 g, 15 mmol) and N₂H₄·H₂O (2 ml, 30 mmol) are dissolved in AcOH (15 ml) and water (10 ml). The solution was boiled under reflux for 1.5 hr, and poured into aqueous NaHCO₃, extracted with EtOAc (100 ml 4) and wash with brine (300 ml). The combined extracts are dried with anhydrous Na₂SO₄, filtered and concentrated. The residue was purified by column chromatography on silica gel (PE/EtOAc = 5/1) to afford the title compound (2.32 g, 72% yield) as a pale yellow solid.

15 Synthesis of 4-(4-methoxyphenyl)pyridazin-3(2H)-one (**115E**):

A solution of Br₂ (0.4 ml) in AcOH (1 ml) was added during 2 min to a stirred solution of Compound 115D (1.22 g, 6 mmol) in AcOH (7 ml) at 70 °C, which was then poured into aqueous NaHCO₃, extracted with DCM (100 ml 4) and wash with brine (400 ml). The combined extracts are dried with anhydrous Na₂SO₄, filtered and concentrated. The residue was purified by column chromatography on silica gel (PE/EtOAc = 2/1) to afford the title compound (0.89 g, 74% yield) as a yellow solid.

Synthesis of 3-chloro-4-(4-methoxyphenyl)pyridazine (**115F**):

25 A solution of Compound 115E (0.89 g, 4.4 mmol, 1.0 eq) in POCl₃ (15 ml) and 3 drops pyridine was boiled under reflux for 3 h. After cooling, the solution was poured onto ice and extracted with DCM (100 ml 4) and wash with aqueous NaHCO₃ (500 ml) and brine (500 ml). The combined extracts are dried with anhydrous Na₂SO₄, filtered and concentrated. The residue was purified by column chromatography on silica gel (PE/EtOAc = 3/1) to afford the title compound (0.69 g, 71% yield) as a pale yellow solid. ¹H NMR (300 MHz, CDCl₃): δ 3.89 (3H, s), 7.05 (2H, d), 7.45 (1H, d), 7.50 (2H, d), 9.13 (1H, d); MS (*m/z*) 613 [M+H]⁺.

Synthesis of 4-(4-methoxyphenyl)pyridazine-3-carbonitrile (**115G**):

To **115F** (395 mg, 1.8 mmol) dissolved in DMF (18 mL) was added Zn(CN)₂ (388 mg, 3.3

mmol) and Pd(PPh₃)₄ (50 mg, 0.44 mmol). The mixture was degassed by alternating vacuum / N₂ purge (3x) and the reaction heated to 100 °C. After 2 h, the reaction was cooled to ambient temperature, filtered over celite, and the eluent was concentrated. The residue was partitioned between EtOAc and H₂O. The organics separated, washed with saturated aqueous NaCl, and dried. After removal of solvent in vacuo, the residue was purified by column chromatography on silica to provide 350 mg of the title compound: ¹H NMR (400 MHz, cdcl₃) δ 9.30 (d, *J* = 5.6 Hz, 1H), 7.66 – 7.57 (m, 3H), 7.24 (s, 1H), 7.12 – 7.05 (m, 2H), 3.89 (s, 3H). . MS (*m/z*) 212.2 [M+H]⁺.

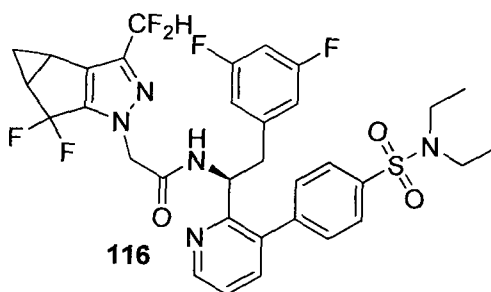
10 Synthesis of 5-(3-(1-amino-2-(3,5-difluorophenyl)ethyl)pyridazin-4-yl)-2-fluorobenzamide (**115H**):

We envision Compound 115G may be further elaborated to the amine compound **115H** in the manner described for an analogous pyridine compound **1B** in Example 1. Alternatively, we envision Compound 115G may be further elaborated to the amine compound **115H** in the manner described for an analogous pyrazine compound **443B** in Example 443

Synthesis of 5-(3-(2-(3,5-difluorophenyl)-1-(2-(3-(trifluoromethyl)-4,5,6,7-tetrahydro-1H-indazol-1-yl)acetamido)ethyl)pyridazin-4-yl)-2-fluorobenzamide (**115I**):

In a manner analogous to the synthesis of Example 589, we envision the title compound may be synthesized utilizing 2-(3-(trifluoromethyl)-4,5,6,7-tetrahydro-1H-indazol-1-yl)acetic acid and substituting **115H** for **54B**.

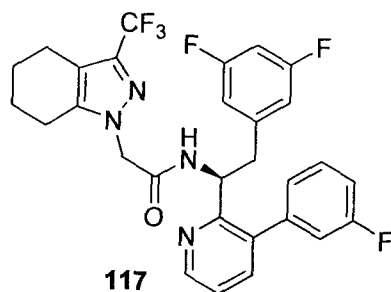
Example 116



25 Synthesis of (S)-N-(1-(3-(4-(N,N-diethylsulfamoyl)phenyl)-pyridin-2-yl)-2-(3,5-difluorophenyl)ethyl)-2-(3-(difluoromethyl)-5,6-dihydro-4,5-(methano)-6,6-difluorocyclopenta[c]pyrazol-1(4H)-yl)acetamide (**116**):

Prepared 14 mg of the title compound by a method analogous to **68B** using **68A** and 4-(N,N-diethylsulfamoyl)phenylboronic acid. MS (*m/z*) 692 [M+H]⁺.

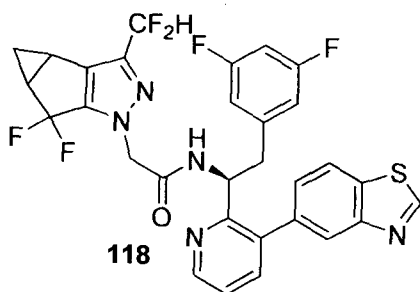
Example 117



Synthesis of (S)-N-(2-(3,5-difluorophenyl)-1-(3-(3-fluorophenyl)pyridin-2-yl)ethyl)-2-(3-(trifluoromethyl)-4,5,6,7-tetrahydro-1H-indazol-1-yl)acetamide (**117**):

Prepared 11.2 mg of the title compound by a method analogous to compound **57B** using **57A** and 3-fluorophenyl boronic acid. MS (m/z) 559 $[M+H]^+$.

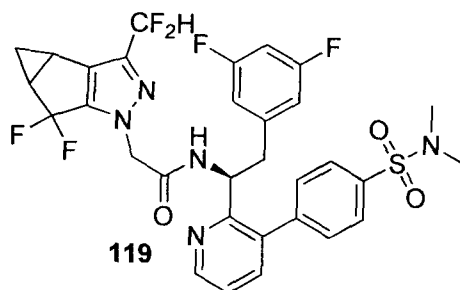
Example 118



Synthesis of (S)-N-(1-(3-(benzo[d]thiazole-5-yl)-pyridin-2-yl)-2-(3,5-difluorophenyl)ethyl)-2-(3-(difluoromethyl)-5,6-dihydro-4,5-(methano)-6,6-difluoro-cyclopenta[c]pyrazol-1(4H)-yl)acetamide (**118**):

Prepared 11.1 mg of the title compound by a method analogous to **68B** using **68A** and 5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzo[d]thiazole. MS (m/z) 612 $[M+H]^+$.

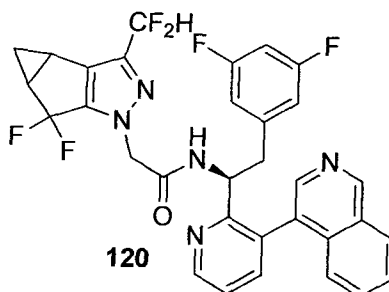
Example 119



Synthesis of (S)-N-(1-(3-(4-(N,N-dimethylsulfamoyl)phenyl)-pyridin-2-yl)-2-(3,5-difluorophenyl)ethyl)-2-(3-(difluoromethyl)-5,6-dihydro-4,5-(methano)-6,6-difluoro-cyclopenta[c]pyrazol-1(4H)-yl)acetamide (**119**):

Prepared 17.3 mg of the title compound by a method analogous to **68B** using **68A** and 4-(N,N-dimethylsulfamoyl)phenylboronic acid. MS (m/z) 664 $[M+H]^+$.

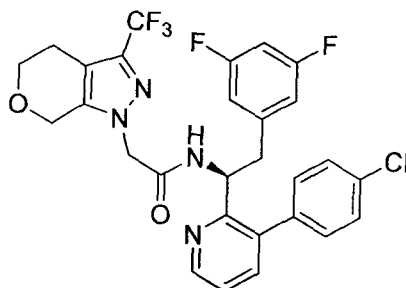
Example 120



Synthesis of 2-(3-(difluoromethyl)-5,5-difluoro-3b,4,4a,5-tetrahydro-1H-cyclopropa[3,4]cyclopenta[1,2-c]pyrazol-1-yl)-N-((S)-2-(3,5-difluorophenyl)-1-(3-(isoquinolin-4-yl)pyridin-2-yl)ethyl)acetamide (**120**):

Prepared 6.1 mg of the title compound by a method analogous to **68B** using **68A** and 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)isoquinoline. MS (m/z) 608 $[M+H]^+$.

Example 121



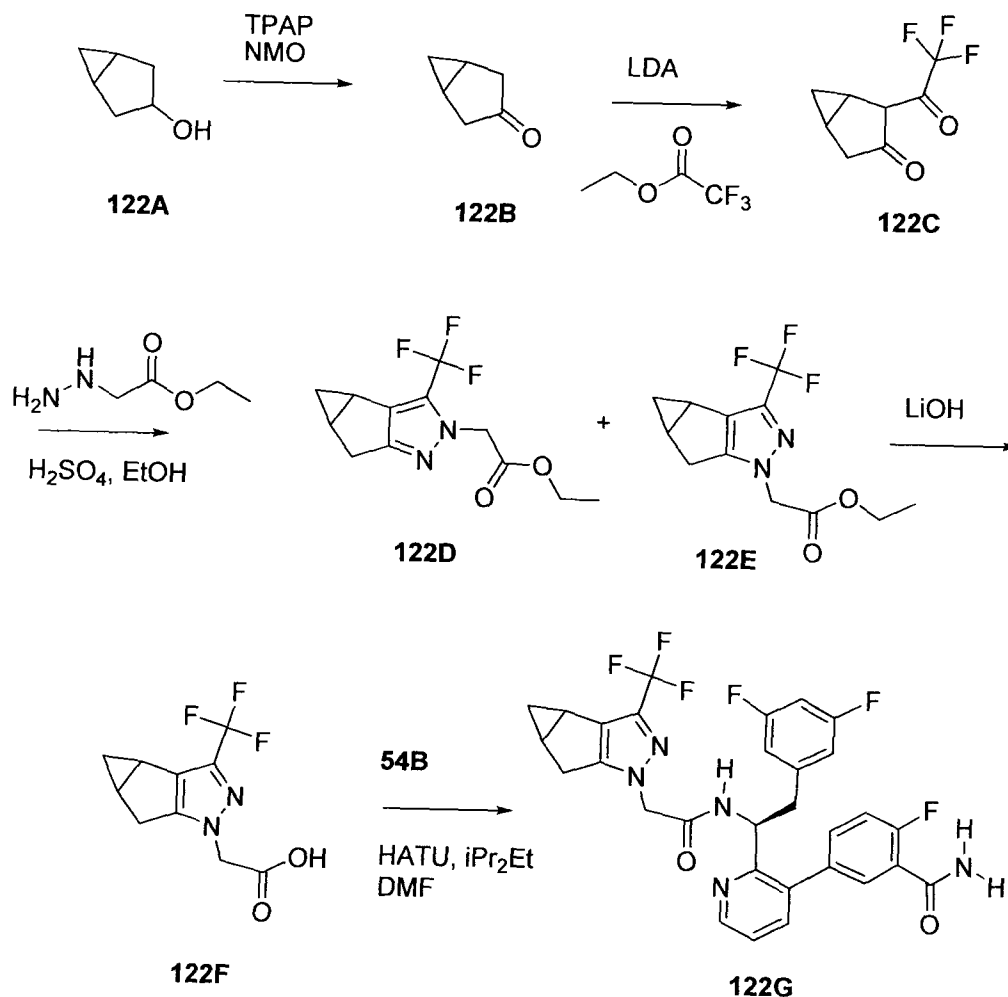
121

Synthesis of (S)-N-(1-(3-(4-chlorophenyl)pyridin-2-yl)-2-(3,5-difluorophenyl)ethyl)-2-(3-(trifluoromethyl)-4,5-dihydropyrano[3,4-c]pyrazol-1(7H)-yl)acetamide (**121**):

The title compound was prepared (22 mg) according to the method presented in the synthesis of Example 36 utilizing **36E** and 2-(3-(trifluoromethyl)-4,5-dihydropyrano[3,4-c]pyrazol-1(7H)-yl)acetic acid. ^1H NMR (400 MHz, dmsO) δ 8.95 (s, 1H), 8.61 (s, 1H), 7.50 (s, 1H), 7.44 – 7.28 (m, 3H), 7.19 – 7.03 (m, 2H), 6.89 (s, 1H), 6.44 – 6.31 (m, 2H), 5.10 (s, 1H), 4.74 – 4.64 (m,

3H), 4.51 – 4.30 (m, 4H), 3.72 – 3.59 (m, 4H), 2.95 – 2.85 (m, 2H), 2.62 – 2.47 (m, 3H), 2.24 (s, 1H), 1.87 – 1.76 (m, 1H). MS (m/z) 577.5 $[M+H]^+$.

Example 122



Synthesis of bicyclo[3.1.0]hexan-3-one (**122B**):

To bicyclo[3.1.0]hexan-3-ol (2 g, 20.4 mmol) dissolved in DCM (40 mL) was added NMO (2.99 g, 25.5 mmol) and 4Å molecular sieves (~4 g). The reaction mixture was cooled to 0 °C and TPAP (144 mg, 2 mol %) added. After 10 min, the reaction was let warm to ambient temperature and stirred for 3 h. The reaction was filtered over celite, eluted with DCM and the eluent purified by column chromatography on silica. The desired fractions were combined, washed with aqueous 1 N HCl (3x), dried with sodium sulfate, and solvents removed in vacuo to provide the title compound.

Synthesis of 2-(2,2,2-trifluoroacetyl)bicyclo[3.1.0]hexan-3-one (**122C**):

Bicyclo[3.1.0]hexan-3-one (2.18 g, 22.7 mmol) was dissolved in THF (150 mL) and cooled to –78 °C upon which LDA (2.0 M, 11.5 mL) was added and stirred 15 min at –78 °C. Ethyl 2,2,2-trifluoroacetate (2.96 mL, 25 mmol) was added dropwise and the reaction stirred 30 at –78 °C and then let warm to room temperature. After 3 h at room temperature, the reaction was judged
5 complete by LCMS. The reaction was quenched with aqueous 1 N HCl and then partitioned between EtOAc and aqueous citric acid. The organics were separated and dried with saturated aqueous NaCl. Solvents were removed in vacuo to provide the title compound (3.74 g).

Synthesis of ethyl 2-(3-(trifluoromethyl)-3b,4,4a,5-tetrahydro-1H-cyclopropa[3,4]cyclopenta[1,2-c]pyrazol-2-yl)acetate (**122D**) and ethyl 2-(3-(trifluoromethyl)-3b,4,4a,5-tetrahydro-1H-cyclopropa[3,4]cyclopenta[1,2-c]pyrazol-1-yl)acetate (**122E**):
10 2-(2,2,2-trifluoroacetyl)bicyclo[3.1.0]hexan-3-one (1 g, 5.2 mmol) was dissolved in EtOH (10 mL) to which sulfuric acid (0.1 mL) was added. 2-hydrazinyl acetic acid ethyl ester hydrochloride (0.805 g, 5.2 mmol) was added and the reaction mixture was heated to 85 °C.
15 After 30 min, LCMS shows complete conversion to pyrazole product. After cooling to room temperature, the reaction was neutralized by the addition of 2N aqueous NaOH. The reaction was concentrated in vacuo and the residue was partitioned between EtOAc and water. The organics were separated, washed with saturated aqueous NaHCO₃, dried with saturated aqueous NaCl, and solvents removed in vacuo. NMR indicated the crude product was a mixture of **122D**
20 and the title compound **122E** as a ratio of 1:5.5. The regioisomers were separable by column chromatography on silica to provide **122D** (MS (*m/z*) 275.1 [M+H]⁺) and the title compound **122E** (720 mg, MS (*m/z*) 275.1 [M+H]⁺).

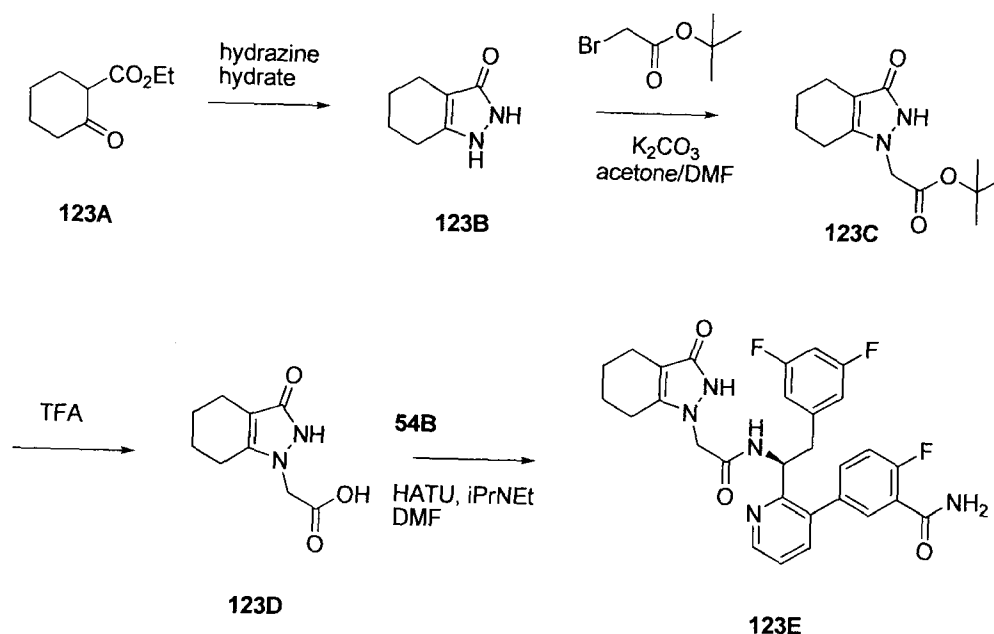
Synthesis of 2-(3-(trifluoromethyl)-3b,4,4a,5-tetrahydro-1H-cyclopropa[3,4]cyclopenta[1,2-c]pyrazol-1-yl)acetic acid (**122F**):
25 Ethyl 2-(3-(trifluoromethyl)-3b,4,4a,5-tetrahydro-1H-cyclopropa[3,4]cyclopenta[1,2-c]pyrazol-1-yl)acetate (145 mg, 0.53 mmol) was dissolved in a mixture of THF (3 mL) and MeOH (1 mL) and treated with LiOH (19 mg, 0.8 mmol) dissolved in H₂O (1 mL). After stirring 3 h at ambient temperature, the mixture was partitioned between EtOAc and 20% aqueous KH₂PO₄. The
30 organics were separated, dried, and removed in vacuo to provide the title compound.

Synthesis of 5-(2-((1S)-2-(3,5-difluorophenyl)-1-(2-(3-(trifluoromethyl)-3b,4,4a,5-tetrahydro-1H-cyclopropa[3,4]cyclopenta[1,2-c]pyrazol-1-yl)acetamido)ethyl)pyridin-3-yl)-2-fluorobenzamide (**122G**):

Compound **122G** was prepared according to the method presented in the synthesis of Example

54 utilizing **54B** and **122F** to provide the title compound (46 mg): ^1H NMR (400 MHz, dmsO) δ 8.91 (d, 1H), 8.66 (s, 1H), 7.75 – 7.56 (m, 3H), 7.49 – 7.37 (m, 3H), 7.36 – 7.25 (m, 1H), 6.91 (d, 1H), 6.64 – 6.41 (m, 3H), 5.15 (d, 2H), 4.66 (dd, 3H), 2.99 (t, 2H), 2.64 (s, 1H), 2.55 (d, 2H), 2.49 – 2.42 (m), 2.29 (s, 1H), 2.00 (s, 2H), 1.02 (d, 1H), 0.12 (s, 1H). MS (m/z) 600.4 [$\text{M}+\text{H}$] $^+$.

10 Example 123



Synthesis of 4,5,6,7-tetrahydro-1H-indazol-3(2H)-one (**123B**):

15 Ethyl 2-oxocyclohexanecarboxylate (5 mL, 29.4 mmol) was combined with hydrazine hydrate (1.47 mL, 29.4 mmol) in EtOH (60 mL) and heated to reflux. After 6 h, the reaction was cooled to ambient temperature and white precipitate was filtered to obtain pure title compound. MS (m/z) 139.13 [$\text{M}+\text{H}$] $^+$.

Synthesis of tert-butyl 2-(3-oxo-2,3,4,5,6,7-hexahydro-1H-indazol-1-yl)acetate (**123C**):

20 4,5,6,7-Tetrahydro-1H-indazol-3(2H)-one (300 mg, 2.17 mmol) was combined with tert-butyl 2-bromoacetate (0.29 mL, 1.96 mmol) and K_2CO_3 (300 mg, 2.17 mmol) in acetone/DMF (25 mL, 4:1). The reaction mixture was stirred at 25 °C for 14 h. Multiple isomers were formed in the

reaction mixture and desired product was isolated by column chromatography on silica (yield: 200 mg): MS (m/z) 253.34 $[M+H]^+$.

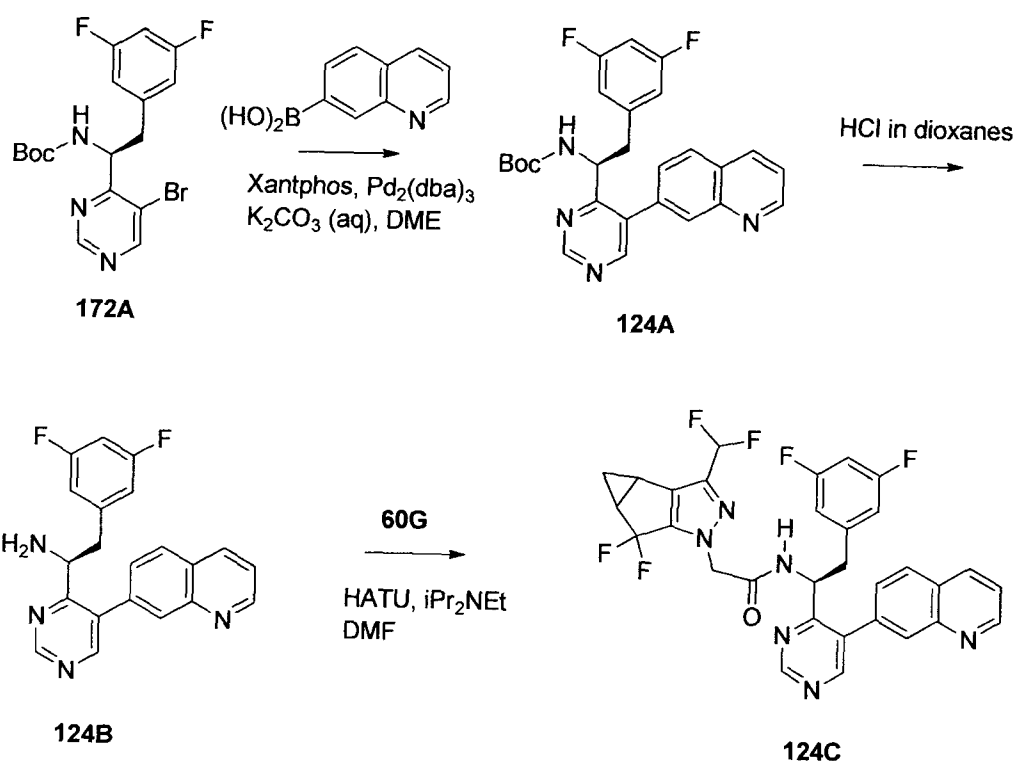
Synthesis of 2-(3-oxo-2,3,4,5,6,7-hexahydro-1H-indazol-1-yl)acetic acid (**123D**):

- 5 tert-Butyl 2-(3-oxo-2,3,4,5,6,7-hexahydro-1H-indazol-1-yl)acetate (30 mg, 0.119 mmol) was dissolved in DCM (0.6 mL) and treated with TFA (0.6 mL). The reaction was stirred for 1.5 h at ambient temperature at which time solvents were removed in vacuo to provide the desired product: MS (m/z) 197.16 $[M+H]^+$.

- 10 Synthesis of (S)-5-(2-(2-(3,5-difluorophenyl)-1-(2-(3-oxo-2,3,4,5,6,7-hexahydro-1H-indazol-1-yl)acetamido)ethyl)pyridin-3-yl)-2-fluorobenzamide (**123E**):

The title compound was prepared (24 mg) according to the method presented in the synthesis of Example 54G utilizing **54B** and 2-(3-oxo-2,3,4,5,6,7-hexahydro-1H-indazol-1-yl)acetic acid. ^1H NMR (400 MHz, cd_3od) δ 8.69 (dd, 1H), 7.62 (dd, 1H), 7.50 (d, 1H), 7.42 (dd, 1H), 7.38 – 7.17 (m, 2H), 6.75 – 6.61 (m, 1H), 6.33 (d, 2H), 5.34 (t, 1H), 4.85 (s, 1H), 4.66 (d, 2H), 3.29 (dt, 8H), 3.16 – 2.98 (m, 2H), 2.39 (dt, Hz, 3H), 1.99 – 1.51 (m, 4H), 1.45 (s, 1H). MS (m/z) 550.5 $[M+H]^+$.

Example 124



Synthesis of (S)-tert-butyl 2-(3,5-difluorophenyl)-1-(5-(quinolin-7-yl)pyrimidin-4-yl)ethylcarbamate (**124A**):

The title compound as prepared according to the method presented in the synthesis of **136B** in Example 136 utilizing **172A** and quinolin-7-ylboronic acid to provide the title compound. MS (m/z) 463.1 $[M+H]^+$.

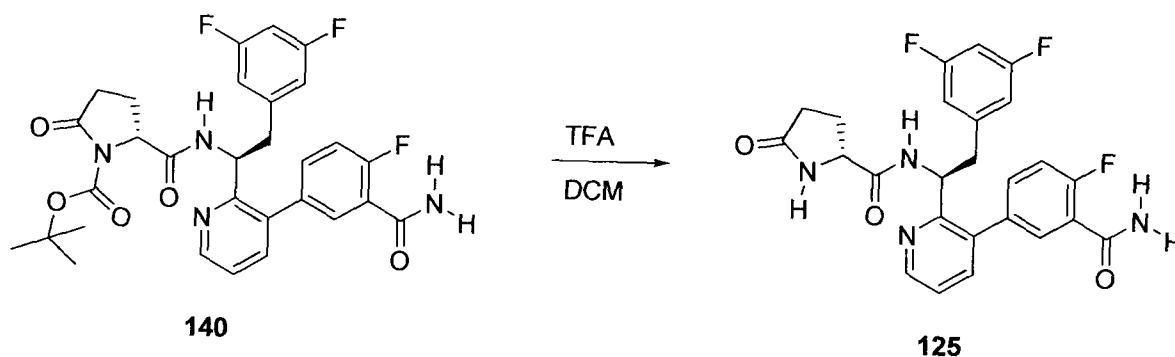
Synthesis of (S)-2-(3,5-difluorophenyl)-1-(5-(quinolin-7-yl)pyrimidin-4-yl)ethanamine (**124B**):

The title compound as prepared according to the method presented in the synthesis of **136C** in Example 136 utilizing (S)-tert-butyl 2-(3,5-difluorophenyl)-1-(5-(quinolin-7-yl)pyrimidin-4-yl)ethylcarbamate to provide the title compound.

Synthesis of 2-(3-(difluoromethyl)-5,5-difluoro-3b,4,4a,5-tetrahydro-1H-cyclopropa[3,4]cyclopenta[1,2-c]pyrazol-1-yl)-N-((S)-2-(3,5-difluorophenyl)-1-(5-(quinolin-7-yl)pyrimidin-4-yl)ethyl)acetamide (**124C**):

The title compound as prepared (20 mg) according to the method presented in the synthesis of Example 54 utilizing **60G** and **124B**. ^1H NMR (400 MHz, dmsO) δ 9.31 (s, 1H), 9.13 (d, 1H), 8.97 (s, 1H), 8.74 (s, 1H), 8.48 (s, 1H), 8.06 (d, 1H), 7.86 (s, 1H), 7.62 (s, 1H), 7.55 (d, 1H), 6.95 – 6.85 (m, 2H), 6.44 (d, 2H), 5.21 (d, 1H), 4.84 – 4.61 (m, 3H), 3.73 (s, 1H), 3.02 (s, 3H), 2.50 – 2.42 (m), 1.35 (s, 1H), 0.87 (s, 1H). MS (m/z) 609.4 $[M+H]^+$.

Example 125



Synthesis of (R)-N-((S)-1-(3-(3-carbamoyl-4-fluorophenyl)pyridin-2-yl)-2-(3,5-difluorophenyl)ethyl)-5-oxopyrrolidine-2-carboxamide (**125**):

Compound 140 (6 mg) was dissolved in DCM (3 mL) and treated with TFA (2 mL). The reaction was stirred for 3 h at ambient temperature at which time solvents were removed in vacuo to provide the title compound (5 mg). MS (m/z) 483.4 $[M+H]^+$.

[illegible]

126

5 The title compound was prepared (19 mg) according to the method presented in the synthesis of Example 54 utilizing **54B** and 1-benzoylpyrrolidine-2-carboxylic acid. MS (*m/z*) 573.4 [M+H]⁺.

127A + **127B** $\xrightarrow[\text{DMF/DMF}]{\text{Pd(PPh}_3)_2\text{Cl, Na}_2\text{CO}_3, \text{LiCl}}$ **127C**

127C $\xrightarrow{\text{HCl in dioxanes}}$ **127B**

127B + **60G** $\xrightarrow[\text{DMF}]{\text{HATU, iPr}_2\text{NEt}}$ **127C**

The title compound as prepared according to the method presented in the synthesis of **68B** in Example 68 utilizing **172A** and 1H-benzo[d]imidazol-4-ylboronic acid to provide the title compound. MS (*m/z*) 452.2 [M+H]⁺.

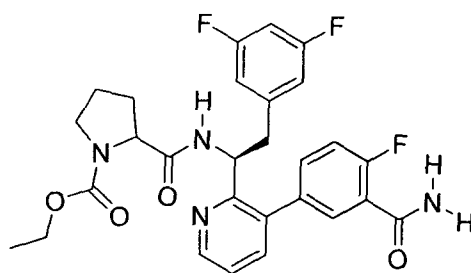
Synthesis of (S)-1-(5-(1H-benzo[d]imidazol-4-yl)pyrimidin-4-yl)-2-(3,5-difluorophenyl)ethanamine (**127B**):

The title compound as prepared according to the method presented in the synthesis of **136C** in Example 136 utilizing (S)-tert-butyl 1-(5-(1H-benzo[d]imidazol-4-yl)pyrimidin-4-yl)-2-(3,5-difluorophenyl)ethylcarbamate to provide the title compound.

Synthesis of N-((S)-1-(5-(1H-benzo[d]imidazol-4-yl)pyrimidin-4-yl)-2-(3,5-difluorophenyl)ethyl)-2-(3-(difluoromethyl)-5,5-difluoro-3b,4,4a,5-tetrahydro-1H-cyclopropa[3,4]cyclopenta[1,2-c]pyrazol-1-yl)acetamide (**127C**):

The title compound as prepared (9 mg) according to the method presented in the synthesis of Example 54 utilizing **60G** and **127B**. ¹H NMR (400 MHz, cd₃od) δ 9.36 (s, 1H), 9.20 (s, 1H), 8.72 (s, 1H), 7.90 (d, 1H), 7.65 (s, 1H), 6.82 (s, 1H), 6.68 (s, 2H), 6.54 (s, 1H), 6.31 (s, 3H), 4.86 (s), 4.77 (s, 3H), 3.29 (dt), 3.06 (d, 3H), 2.97 (s, 1H), 2.84 (s, 1H), 2.44 (s, 3H), 1.35 (s, 1H), 1.01 (s, 2H), 0.08 (s, 1H). MS (*m/z*) 598.3 [M+H]⁺.

Example 128

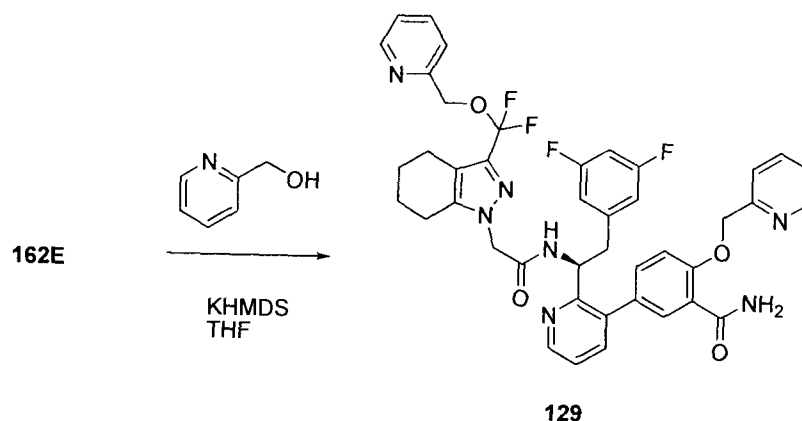


128

Synthesis of ethyl 2-((S)-1-(3-(3-carbamoyl-4-fluorophenyl)pyridin-2-yl)-2-(3,5-difluorophenyl)ethylcarbamoyl)pyrrolidine-1-carboxylate (**128**):

The title compound was prepared (9 mg) according to the method presented in the synthesis of Example 54 utilizing **54B** and 1-(ethoxycarbonyl)pyrrolidine-2-carboxylic acid.

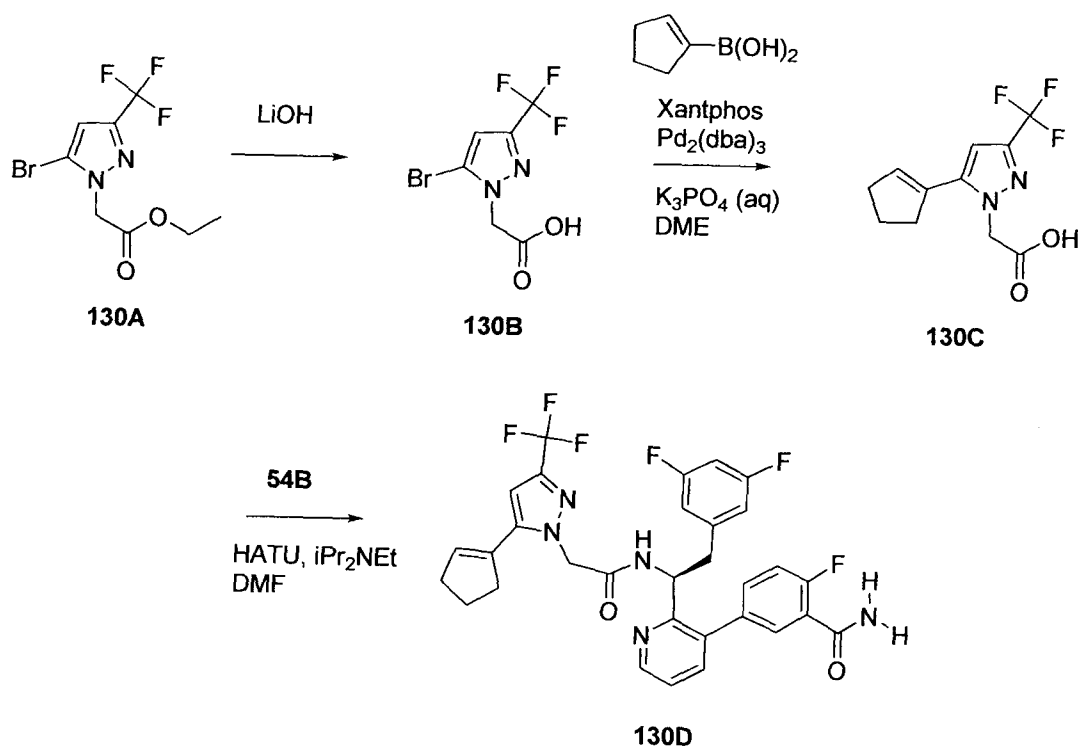
Example 129



Synthesis of (S)-5-(2-(1-(2-(3-(difluoro(pyridin-2-ylmethoxy)methyl)-4,5,6,7-tetrahydro-1H-indazol-1-yl)acetamido)-2-(3,5-difluorophenyl)ethyl)pyridin-3-yl)-2-(pyridin-2-ylmethoxy)benzamide (**129**):

- 5 The title compound was prepared (2 mg) according to the method presented in the synthesis of Example 159 utilizing **162E** and pyridin-2-ylmethanol. ¹H NMR (400 MHz, dmsO) δ 8.80 (d, J = 8.6 Hz, 1H), 8.60 (dd, J = 26.7, 10.9 Hz, 2H), 8.03 (s, 1H), 7.85 (dd, J = 15.6, 7.9 Hz, 1H), 7.71 – 7.56 (m, 2H), 7.50 – 7.32 (m, 3H), 7.25 (d, J = 8.5 Hz, 1H), 6.91 (s, 1H), 6.61 (d, J = 6.5 Hz, 2H), 5.39 (s, 1H), 5.22 (d, J = 6.7 Hz, 1H), 5.00 (s, 1H), 4.63 (d, J = 3.4 Hz, 2H), 3.87 (s, 2H), 3.00 (s, 2H), 2.63 (s, 1H), 2.51 – 2.28 (m, 20H), 2.12 (s, 1H), 1.56 (s, 3H). MS (m/z) 780.3 [M+H]⁺.
- 10

Example 130



Synthesis of 2-(5-bromo-3-(trifluoromethyl)-1H-pyrazol-1-yl)acetic acid (**130B**):

The title compound was prepared according to the method presented in the synthesis of **122F** in Example 122 utilizing ethyl 2-(5-bromo-3-(trifluoromethyl)-1H-pyrazol-1-yl)acetate (synthesized as described in WO 2008/13622).

5

Synthesis of 2-(5-cyclopentenyl-3-(trifluoromethyl)-1H-pyrazol-1-yl)acetic acid (**130C**):

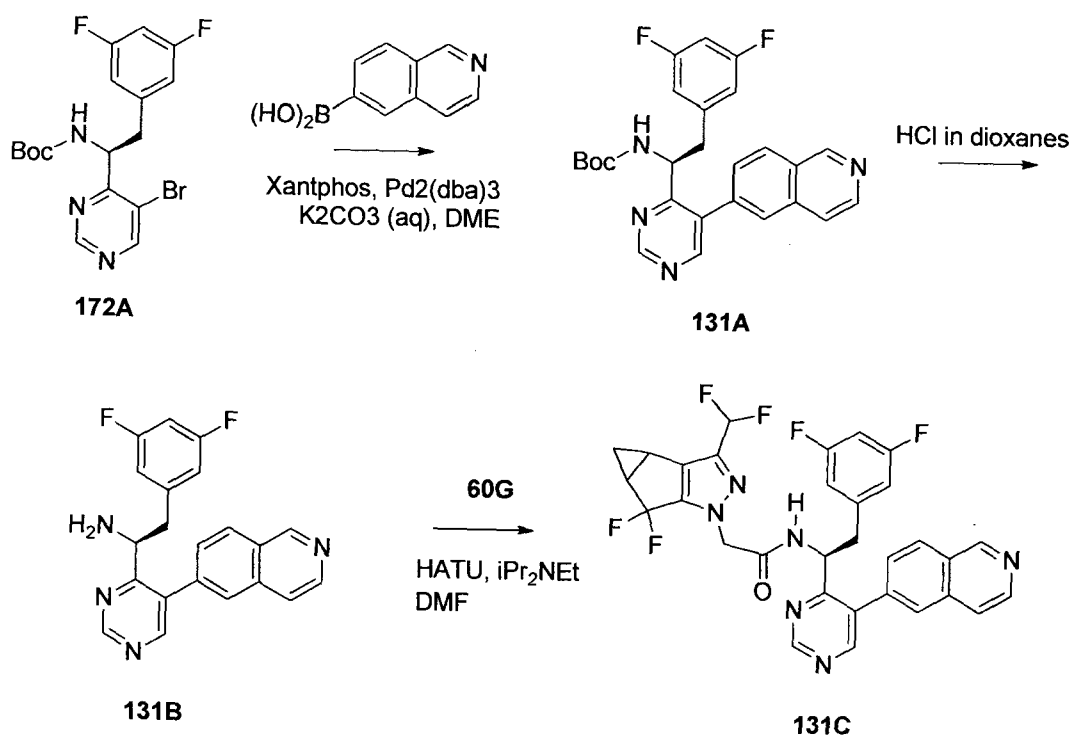
In a microwave vial, 2-(5-bromo-3-(trifluoromethyl)-1H-pyrazol-1-yl)acetic acid (60 mg, 0.22 mmol), cyclopentenylboronic acid (49 mg, 0.44 mmol), Xantphos (13 mg), Pd₂(dba)₃ (10 mg), and 2M aq K₃PO₄ (0.24 mL) were combined in DME (2.2 mL). The reaction was heated in a microwave reactor at 180 °C for 40 min. The reaction mixture was filtered and solvents removed in vacuo. The residue was partitioned between aqueous saturated NaHCO₃ and EtOAc. The aqueous layer was then acidified with 1N aq HCl and extracted with EtOAc. The organics were washed, dried, and removed in vacuo to provide the title compound. MS (*m/z*) 573.4 [M+H]⁺.

10

15 Synthesis of (S)-5-(2-(1-(2-(5-cyclopentenyl-3-(trifluoromethyl)-1H-pyrazol-1-yl)acetamido)-2-(3,5-difluorophenyl)ethyl)pyridin-3-yl)-2-fluorobenzamide (**130D**):

The title compound was prepared (7 mg) according to the method presented in the synthesis of Example 54 utilizing **54B** and **130C**. MS (*m/z*) 614.4 [M+H]⁺.

20 Example 131



Synthesis of (S)-tert-butyl 2-(3,5-difluorophenyl)-1-(5-(isoquinolin-6-yl)pyrimidin-4-yl)ethylcarbamate (**131A**):

The title compound as prepared according to the method presented in the synthesis of **136B** in Example 136 utilizing **172A** and isoquinolin-6-ylboronic acid to provide the title compound. MS (m/z) 463.1 $[M+H]^+$.

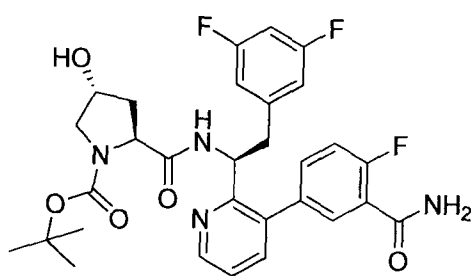
Synthesis of (S)-2-(3,5-difluorophenyl)-1-(5-(isoquinolin-6-yl)pyrimidin-4-yl)ethanamine (**131B**):

The title compound as prepared according to the method presented in the synthesis of **136C** in Example 136 utilizing (S)-tert-butyl 2-(3,5-difluorophenyl)-1-(5-(isoquinolin-6-yl)pyrimidin-4-yl)ethylcarbamate to provide the title compound.

Synthesis of 2-(3-(difluoromethyl)-5,5-difluoro-3b,4,4a,5-tetrahydro-1H-cyclopropa[3,4]cyclopenta[1,2-c]pyrazol-1-yl)-N-((S)-2-(3,5-difluorophenyl)-1-(5-(isoquinolin-6-yl)pyrimidin-4-yl)ethyl)acetamide (**131C**):

The title compound as prepared (26 mg) according to the method presented in the synthesis of Example 54 utilizing **60G** and **131B**. ^1H NMR (400 MHz, dmso) δ 9.60 (s, 1H), 9.35 (s, 1H), 9.15 (s, 1H), 8.75 (d, 1H), 8.62 (d, 1H), 8.35 (d, 1H), 8.02 (s, 1H), 7.80 (s, 2H), 6.98 – 6.88 (m, 2H), 6.79 (s, 1H), 6.47 (d, 2H), 5.25 – 5.05 (m, 2H), 4.83 – 4.63 (m, 4H), 3.05 (d, 2H), 2.50 – 2.41 (m), 1.34 (s, 1H), 0.87 (s, 1H). MS (m/z) 609.4 $[M+H]^+$.

Example 132

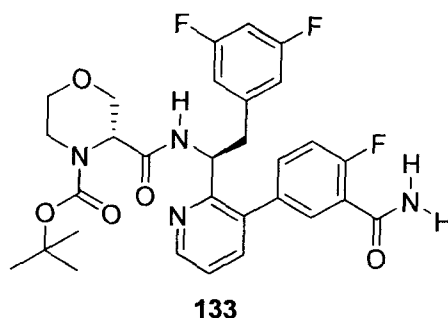


132

Synthesis of (2S,4R)-tert-butyl 2-((S)-1-(3-(3-carbamoyl-4-fluorophenyl)pyridin-2-yl)-2-(3,5-difluorophenyl)ethylcarbamoyl)-4-hydroxypyrrolidine-1-carboxylate (**132**):

The title compound was prepared (13 mg) according to the method presented in the synthesis of Example 54 utilizing **54B** and (2S,4R)-1-(tert-butoxycarbonyl)-4-hydroxypyrrolidine-2-carboxylic acid. MS (m/z) 585.1 $[M+H]^+$.

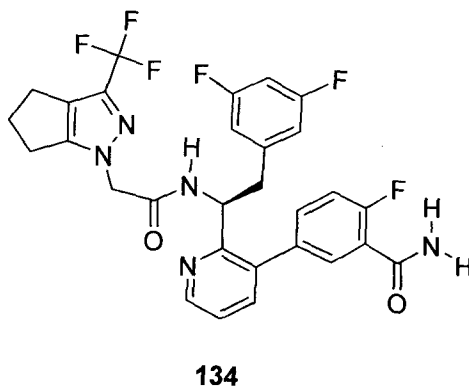
Example 133



Synthesis of (R)-tert-butyl 3-((S)-1-(3-(3-carbamoyl-4-fluorophenyl)pyridin-2-yl)-2-(3,5-difluorophenyl)ethylcarbamoyl)morpholine-4-carboxylate (**133**):

The title compound was prepared (13 mg) according to the method presented in the synthesis of Example 54 utilizing **54B** and (R)-4-(tert-butoxycarbonyl)morpholine-3-carboxylic acid. ¹H NMR (400 MHz, cdcl₃) δ 8.80 (s, 2H), 7.97 (s, 1H), 7.83 (s, 1H), 7.74 (s, 1H), 7.54 (s, 1H), 7.37 – 7.22 (m, 11H), 6.98 (s, 1H), 6.59 (s, 1H), 6.19 (s, 4H), 5.57 (s, 1H), 4.55 (s, 1H), 4.39 (s, 1H), 3.71 (d, 3H), 3.63 – 3.62 (m, 1H), 3.45 (s, 1H), 3.24 (s, 2H), 2.50 (s, 1H), 1.46 (s, 5H).

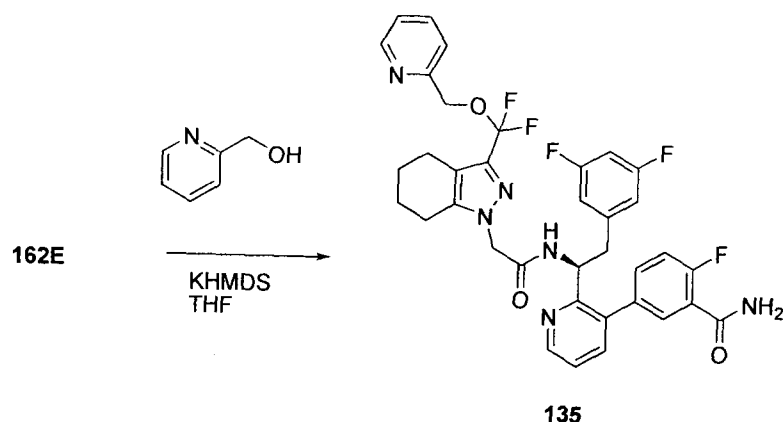
Example 134



Synthesis of (S)-5-(2-(2-(3,5-difluorophenyl)-1-(2-(3-(trifluoromethyl)-5,6-dihydrocyclopenta[c]pyrazol-1(4H)-yl)acetamido)ethyl)pyridin-3-yl)-2-fluorobenzamide (**134**):

The title compound was prepared (7 mg) according to the method presented in the synthesis of Example 56 utilizing **56A** and 3-(trifluoromethyl)-1,4,5,6-tetrahydrocyclopenta[c]pyrazole. ¹H NMR (400 MHz, dmso) δ 8.94 (d, 1H), 8.67 (s, 1H), 7.72 – 7.56 (m, 3H), 7.48 (s, 1H), 7.45 – 7.15 (m, 4H), 6.90 (s, 1H), 6.53 (d, 2H), 5.15 (s, 1H), 4.70 (s, 2H), 3.00 (s, 2H), 2.55 (s, 2H), 2.51 – 2.41 (m). MS (*m/z*) 588.3 [M+H]⁺.

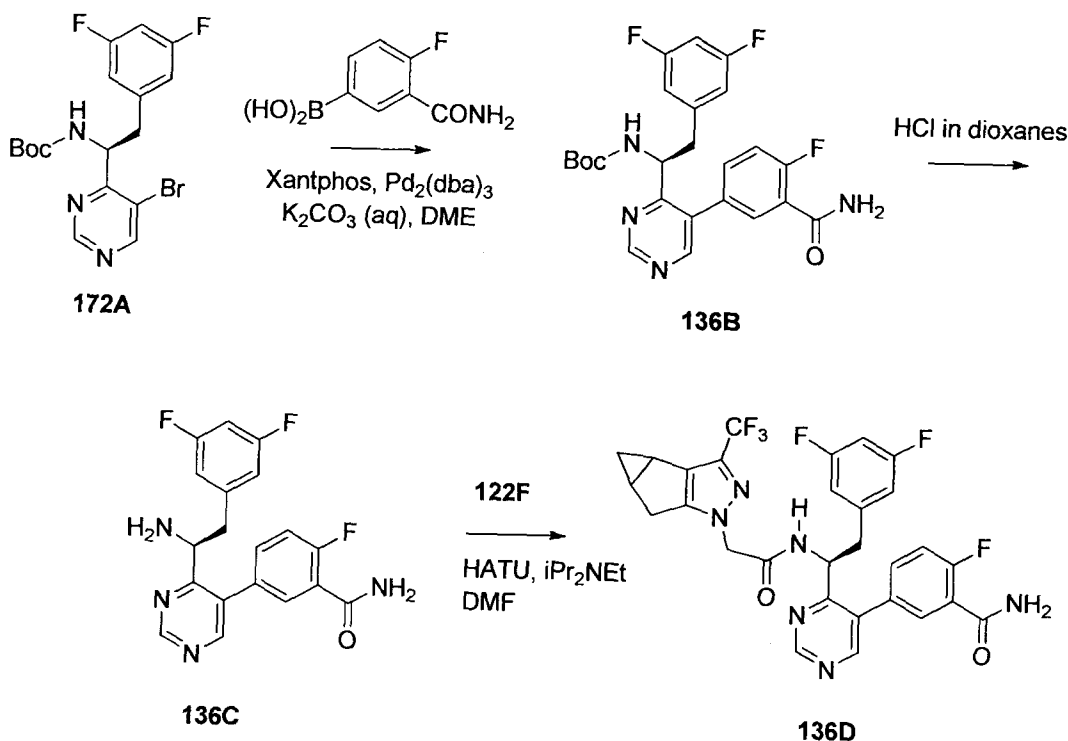
Example 135



Synthesis of (S)-5-(2-(1-(2-(3-(difluoro(pyridin-2-ylmethoxy)methyl)-4,5,6,7-tetrahydro-1H-indazol-1-yl)acetamido)-2-(3,5-difluorophenyl)ethyl)pyridin-3-yl)-2-fluorobenzamide (**135**):

The title compound was prepared (2 mg) according to the method presented in the synthesis of Example 159 utilizing **162E** and pyridin-2-ylmethanol. The title compound exhibited a shorter retention time on HPLC relative to its regioisomer (Compound **143**). ¹H NMR (400 MHz, dmso) δ 8.86 (d, *J* = 8.3 Hz, 1H), 8.66 (d, *J* = 3.0 Hz, 1H), 8.53 (d, *J* = 5.2 Hz, 1H), 7.83 (d, *J* = 8.2 Hz, 1H), 7.76 – 7.56 (m, 2H), 7.52 – 7.21 (m, 4H), 6.91 (s, 1H), 6.55 (d, *J* = 6.6 Hz, 2H), 5.17 (d, *J* = 6.6 Hz, 1H), 4.98 – 4.87 (m, 1H), 4.65 (s, 2H), 4.06 (s, 2H), 2.99 (d, *J* = 7.9 Hz, 2H), 2.52 – 2.41 (m, 18H), 2.39 (s, 1H), 2.37 – 2.30 (m, 1H), 2.22 (d, *J* = 43.0 Hz, 2H), 1.57 (s, 3H). MS (*m/z*) 691.3 [M+H]⁺.

Example 136



Synthesis of (S)-tert-butyl 1-(5-(3-carbamoyl-4-fluorophenyl)pyrimidin-4-yl)-2-(3,5-difluorophenyl)ethylcarbamate (**136B**):

To (S)-tert-butyl 1-(5-bromopyrimidin-4-yl)-2-(3,5-difluorophenyl)ethylcarbamate (250 mg, 0.6 mmol) in DME (3 mL) was added 3-carbamoyl-4-fluorophenylboronic acid (110 mg, 0.6 mmol), Xantphos (35 mg), Pd₂(dba)₃ (28 mg), and aqueous 2M K₂CO₃ (0.45 mL). The reaction was heated to 65 °C for 2d at which time it was diluted with aqueous 1N HCl and extracted with EtOAc. The organics were separated, washed, dried and removed in vacuo. The crude product was purified by column chromatography on silica to provide 130 mg of the title compound. MS (*m/z*) 473.0 [M+H]⁺.

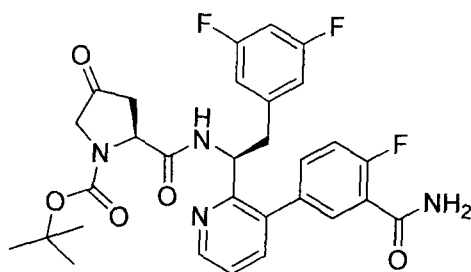
Synthesis of (S)-5-(4-(1-amino-2-(3,5-difluorophenyl)ethyl)pyrimidin-5-yl)-2-fluorobenzamide (**136C**):

(S)-tert-butyl 1-(5-(3-carbamoyl-4-fluorophenyl)pyrimidin-4-yl)-2-(3,5-difluorophenyl)ethylcarbamate (130 mg, 0.28 mmol) was dissolved in DCM (2 mL) and treated with HCl (4 N in dioxanes, 3 mL). After 3 h at ambient temperature, the solvents were removed in vacuo to provide the title compound.

Synthesis of 5-(4-((1S)-2-(3,5-difluorophenyl)-1-(2-(3-(trifluoromethyl)-3b,4,4a,5-tetrahydro-1H-cyclopropa[3,4]cyclopenta[1,2-c]pyrazol-1-yl)acetamido)ethyl)pyrimidin-5-yl)-2-fluorobenzamide(**136D**):

The title compound as prepared (16 mg) according to the method presented in the synthesis of Example 54 utilizing **122F** and **136C**. ¹H NMR (400 MHz, dmso) δ 9.15 (d, 1H), 8.97 (d, 1H), 8.52 (s, 1H), 7.58 (s, 2H), 7.45 (dd, 1H), 7.36 (s, 1H), 7.28 – 7.20 (m, 1H), 6.83 (d, 1H), 6.48 (t, 2H), 5.03 (d, 3H), 4.74 – 4.40 (m, 4H), 2.50 (ddd, 2H), 2.42 – 2.20 (m), 1.91 (s, 2H), 0.99 – 0.73 (m, 1H), 0.01 (s, 1H). MS (*m/z*) 601.2 [M+H]⁺.

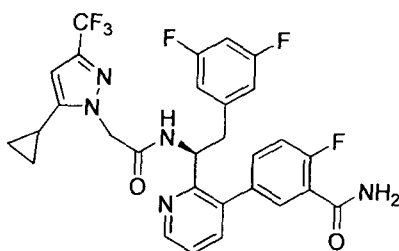
Example 137

**137**

Synthesis of (S)-tert-butyl 2-((S)-1-(3-(3-carbamoyl-4-fluorophenyl)pyridin-2-yl)-2-(3,5-difluorophenyl)ethylcarbamoyl)-4-oxopyrrolidine-1-carboxylate (**137**):

The title compound was prepared (12 mg) according to the method presented in the synthesis of Example 54 utilizing **54B** and (S)-1-(tert-butoxycarbonyl)-4-oxopyrrolidine-2-carboxylic acid. MS (*m/z*) 583.2 [M+H]⁺.

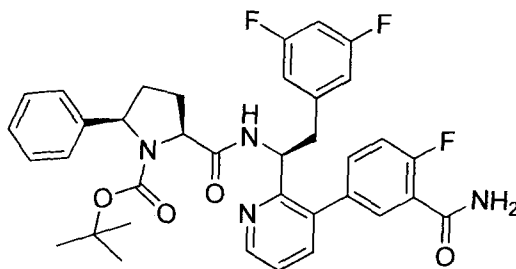
Example 138

**138**

Synthesis of (S)-5-(2-(1-(2-(5-cyclopropyl-3-(trifluoromethyl)-1H-pyrazol-1-yl)acetamido)-2-(3,5-difluorophenyl)ethyl)pyridin-3-yl)-2-fluorobenzamide (**138**):

The title compound was prepared (43 mg) according to the method presented in the synthesis of Example 54 utilizing **54B** and **61C**. ¹H NMR (400 MHz, dmsO) δ 8.96 (d, 1H), 8.71 – 8.64 (m, 1H), 7.77 – 7.57 (m, 3H), 7.55 – 7.32 (m, 3H), 7.29 (d, 1H), 6.91 (t, 1H), 6.56 (d, 2H), 6.28 (s, 1H), 5.19 (d, 2H), 4.86 (s, 2H), 3.11 – 2.81 (m, 3H), 2.52 – 2.42 (m, 20H), 1.87 (s, 1H), 1.47 (t, 1H), 0.74 (d, 2H), 0.59 (s, 1H), 0.53 (s, 1H). MS (*m/z*) 588.6 [M+H]⁺.

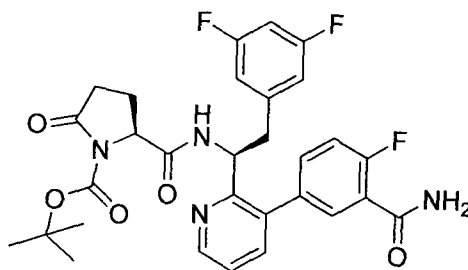
Example 139

**139**

Synthesis of (2S,5R)-tert-butyl 2-((S)-1-(3-(3-carbamoyl-4-fluorophenyl)pyridin-2-yl)-2-(3,5-difluorophenyl)ethylcarbamoyl)-5-phenylpyrrolidine-1-carboxylate (**139**):

The title compound was prepared (9 mg) according to the method presented in the synthesis of Example 54 utilizing **54B** and (2S,5R)-1-(tert-butoxycarbonyl)-5-phenylpyrrolidine-2-carboxylic acid. MS (m/z) 645.1 $[M+H]^+$.

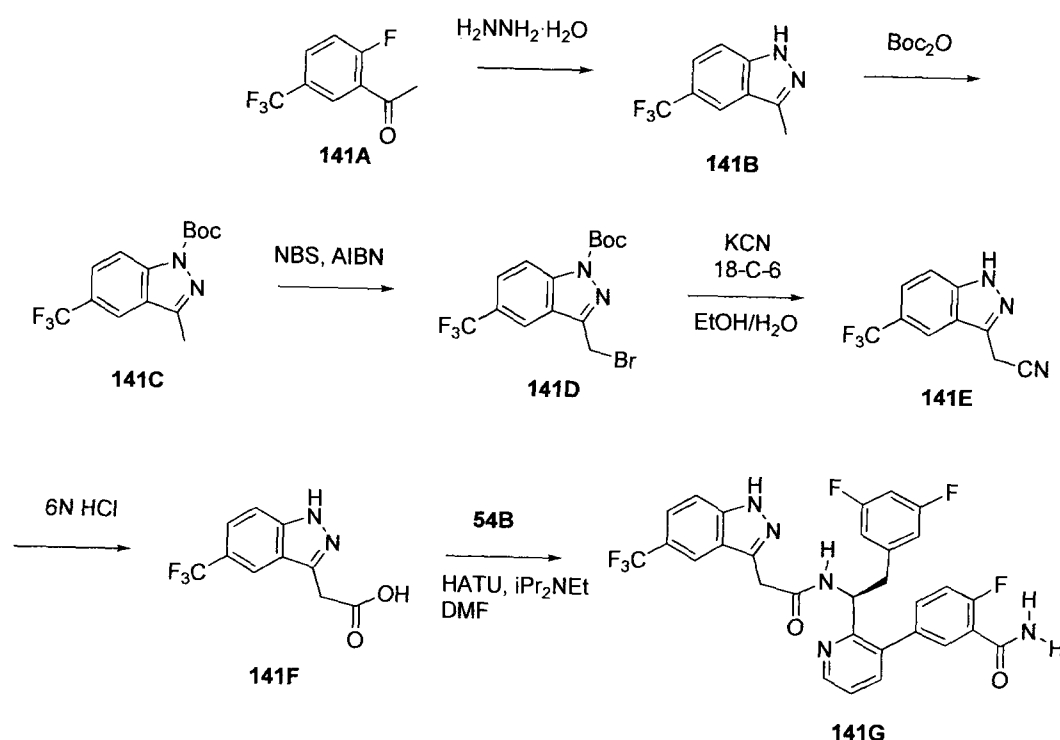
Example 140

**140**

Synthesis of (S)-tert-butyl 2-((S)-1-(3-(3-carbamoyl-4-fluorophenyl)pyridin-2-yl)-2-(3,5-difluorophenyl)ethylcarbamoyl)-5-oxopyrrolidine-1-carboxylate (**140**):

The title compound as prepared (4 mg) according to the method presented in the synthesis of Example 54 utilizing **54B** and (S)-1-(tert-butoxycarbonyl)-5-oxopyrrolidine-2-carboxylic acid. MS (m/z) 583.0 $[M+H]^+$.

Example 141



Synthesis of 3-methyl-5-(trifluoromethyl)-1H-indazole (**141B**):

To 1-(2-fluoro-5-(trifluoromethyl)phenyl)ethanone (12.95 g, 62.9 mmol) in ethylene glycol (33 mL) was added hydrazine hydrate (3.1 mL, 100 mmol). The reaction was heated at 165 °C for 16 h. After cooling to ambient temperature, the reaction solidifies and the solids filtered. The cake was dissolved in DCM, washed with H₂O, and dried over sodium sulfate. Solvents were removed in vacuo to provide 6.75 g of the title compound. MS (*m/z*) 201.0 [*M*+H]⁺.

Synthesis of tert-butyl 3-methyl-5-(trifluoromethyl)-1H-indazole-1-carboxylate (**141C**):

To 3-methyl-5-(trifluoromethyl)-1H-indazole (3 g, 15 mmol) in THF (100 mL) was added Boc₂O (3.27 g, 15 mmol), TEA (2.1 mL, 15 mmol), and DMAP (367 mg, 3 mmol). The reaction was stirred for 2 h then partitioned between EtOAc and saturated aqueous NH₄Cl. Organics were separated, dried, and removed in vacuo to provide 3.8 g of the title compound.

Synthesis of tert-butyl 3-(bromomethyl)-5-(trifluoromethyl)-1H-indazole-1-carboxylate (**141D**):

To tert-butyl 3-methyl-5-(trifluoromethyl)-1H-indazole-1-carboxylate (1.9 g) in carbon tetrachloride (20 mL) was added NBS (1.28 g, 7.2 mmol). The reaction was heated to 90 °C then AIBN (115 mg, 0.7 mmol) was added. After 16 h, additional aliquots of NBS (500 mg) and AIBN (115 mg) were added and the temperature was raised to 110 °C. After 16 h, the reaction was cooled to ambient temperature and solvents removed in vacuo. The crude residue was

partitioned between EtOAc and H₂O. The organics were separated, washed with saturated aqueous NaHCO₃, dried, removed in vacuo. The crude product was purified by column chromatography on silica to provide title compound. MS (*m/z*) 279.0 [M+H]⁺.

5 Synthesis of 2-(5-(trifluoromethyl)-1H-indazol-3-yl)acetonitrile (**141E**):

To tert-butyl 3-(bromomethyl)-5-(trifluoromethyl)-1H-indazole-1-carboxylate (300 mg, 0.79 mmol) dissolved in EtOH (3.5 mL) and H₂O (0.5 mL) was added catalytic 18-C-6 and KCN (51 mg, 0.79 mmol). The reaction was stirred 2 h then the reaction was partitioned between EtOAc and saturated aqueous NaHCO₃. The organics were separated, washed with , saturated aqueous
10 NaHCO₃ dried and removed in vacuo to provide the title compound. MS (*m/z*) 226.0 [M+H]⁺.

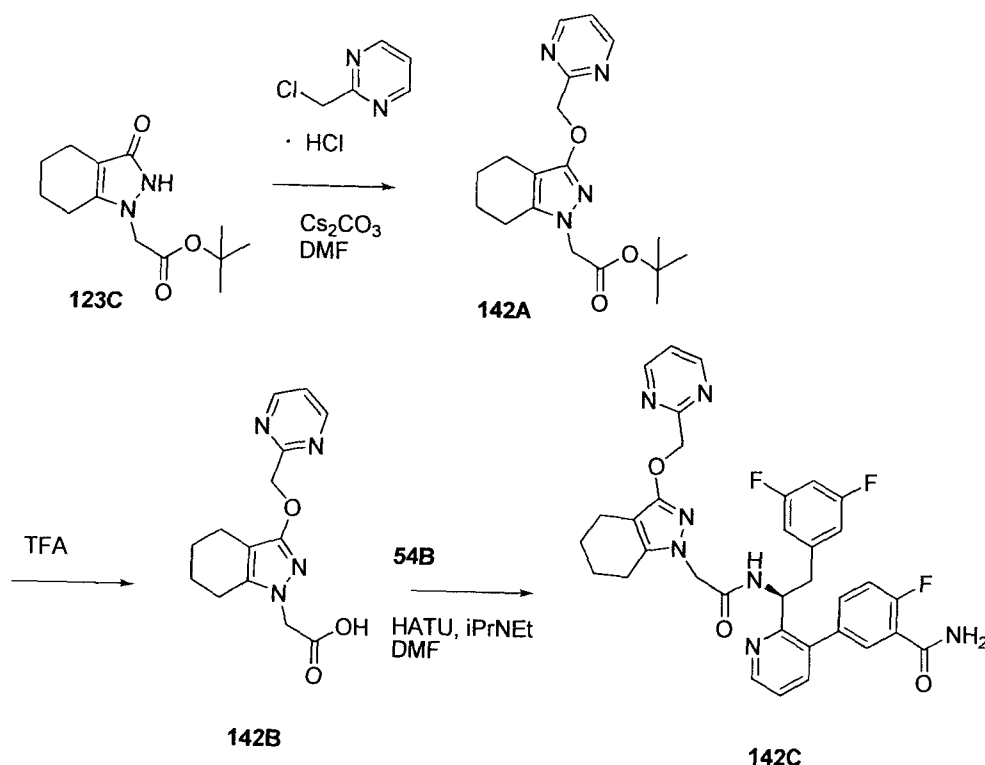
Synthesis of 2-(5-(trifluoromethyl)-1H-indazol-3-yl)acetic acid (**141F**):

2-(5-(trifluoromethyl)-1H-indazol-3-yl)acetonitrile (60 mg) was treated with 6N aqueous HCl (2 mL) and heated to 105 °C for 5 h. The reaction was extracted with EtOAc, organics washed with
15 20% aqueous KH₂PO₄, dried and solvents removed in vacuo to provide 55 mg of the title compound. MS (*m/z*) 245.0 [M+H]⁺.

Synthesis of (S)-5-(2-(2-(3,5-difluorophenyl)-1-(2-(5-(trifluoromethyl)-1H-indazol-3-yl)acetamido)ethyl)pyridin-3-yl)-2-fluorobenzamide (**141G**):

20 The title compound was prepared (13 mg) according to the method presented in the synthesis of Example 54 utilizing **54B** and **141F**. ¹H NMR (400 MHz, dmsO) δ 8.93 (d, 1H), 8.64 (d, 1H), 8.03 (s, 1H), 7.56 (dt, 5H), 7.48 – 7.28 (m, 3H), 7.28 – 7.17 (m, 1H), 6.82 (s, 1H), 6.47 (d, 2H), 5.15 (d, 1H), 3.82 (s, 2H), 2.98 (d, 2H), 2.52 – 2.41 (m). MS (*m/z*) 598.4 [M+H]⁺.

25 Example 142



Synthesis of tert-butyl 2-(3-(pyrimidin-2-ylmethoxy)-4,5,6,7-tetrahydro-1H-indazol-1-yl)acetate (**142A**):

tert-Butyl 2-(3-oxo-2,3,4,5,6,7-hexahydro-1H-indazol-1-yl)acetate (38 mg, 0.15 mmol) was dissolved in DMF (1.5 mL) and treated with 2-(chloromethyl)pyrimidine hydrochloride (27 mg, 0.17 mmol) and Cs₂CO₃ (196 mg, 0.6 mmol). The reaction mixture was stirred 3 hr. The solids were filtered and the filtrate partitioned between EtOAc and H₂O. The organics were dried over saturated aqueous NaCl and removed in vacuo. The crude residue was purified by column chromatography on silica to provide a mixture of N1 and N2 regioisomers that were carried onto the next step: MS (*m/z*) 345.2 [M+H]⁺.

Synthesis of 2-(3-(pyrimidin-2-ylmethoxy)-4,5,6,7-tetrahydro-1H-indazol-1-yl)acetic acid (**142B**):

The title compound was prepared according to the method presented in the synthesis of **170B** in Example 170: MS (*m/z*) 289.2 [M+H]⁺.

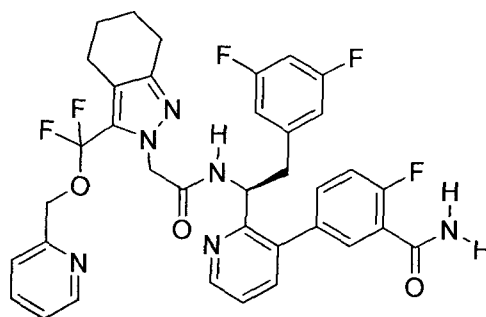
Synthesis of (S)-5-(2-(2-(3,5-difluorophenyl)-1-(2-(3-(pyrimidin-2-ylmethoxy)-4,5,6,7-tetrahydro-1H-indazol-1-yl)acetamido)ethyl)pyridin-3-yl)-2-fluorobenzamide (**142C**):

The title compound was prepared (29 mg) according to the method presented in the synthesis of Example 54 utilizing **54B** and 2-(3-(pyrimidin-2-ylmethoxy)-4,5,6,7-tetrahydro-1H-indazol-1-

yl)acetic acid. The undesired N2 isomer observed in the synthesis of **142A** was removed during purification: ^1H NMR (400 MHz, dmso) δ 8.76 (d, 2H), 8.64 (d, 1H), 8.45 (d, 1H), 7.77 – 7.58 (m, 3H), 7.58 – 7.27 (m, 5H), 6.90 (s, 1H), 6.52 (d, 2H), 5.23 – 5.12 (m, 3H), 4.34 (s, 2H), 2.94 (dd, 2H), 2.53 – 2.41 (m, 20H), 2.22 (s, 3H), 1.87 (s, 1H), 1.56 (s, 5H). MS (m/z) 642.7 $[\text{M}+\text{H}]^+$.

5

Example 143



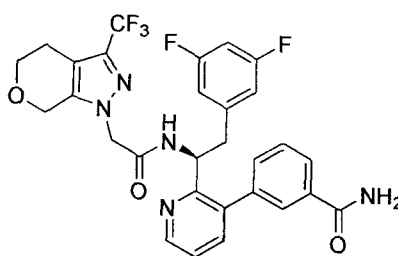
143

Synthesis of (S)-5-(2-(1-(2-(3-(difluoro(pyridin-2-ylmethoxy)methyl)-4,5,6,7-tetrahydro-2H-indazol-2-yl)acetamido)-2-(3,5-difluorophenyl)ethyl)pyridin-3-yl)-2-fluorobenzamide (**143**):

10

The title compound was prepared (1 mg) according to the method presented in the synthesis of Example 159 utilizing **162E** and pyridin-2-ylmethanol. The title compound exhibited a longer retention time on HPLC relative to its regioisomer (Compound 135). MS (m/z) 691.3 $[\text{M}+\text{H}]^+$.

Example 144



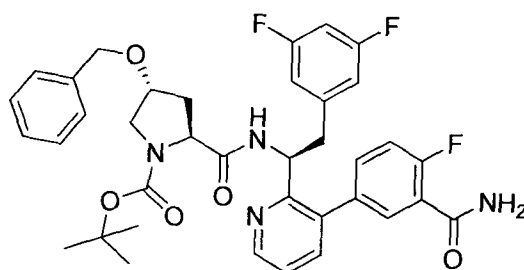
144

Synthesis of (S)-3-(2-(2-(3,5-difluorophenyl)-1-(2-(3-(trifluoromethyl)-4,5-dihydropyrano[3,4-c]pyrazol-1(7H)-yl)acetamido)ethyl)pyridin-3-yl)benzamide (**144**):

The title compound was prepared (31 mg) according to the method presented in the synthesis of Example 50 utilizing **50C** and 2-(3-(trifluoromethyl)-4,5-dihydropyrano[3,4-c]pyrazol-1(7H)-yl)acetic acid. ^1H NMR (400 MHz, dmso) δ 8.99 (d, 1H), 8.68 (s, 1H), 8.01 – 7.84 (m, 2H), 7.71 (s, 1H), 7.64 (d, 1H), 7.45 (dd, 10.1 Hz, 5H), 6.90 (s, 1H), 6.48 (d, 2H), 5.19 (s, 1H), 4.75 (s,

2H), 4.48 (d, 2H), 4.39 (d, 2H), 3.71 (s, 2H), 3.00 (s, 1H), 2.54 (s, 2H), 2.52 – 2.42 (m, 68H), 2.29 (s, 1H). MS (m/z) 586.4 $[M+H]^+$.

Example 145

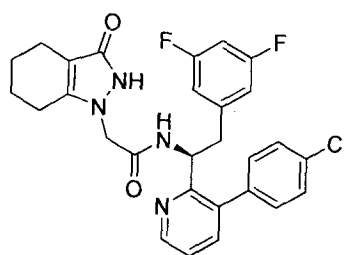


145

Synthesis of (2S,4R)-tert-butyl 4-(benzyloxy)-2-(((S)-1-(3-(3-carbamoyl-4-fluorophenyl)pyridin-2-yl)-2-(3,5-difluorophenyl)ethylcarbamoyl)pyrrolidine-1-carboxylate (**145**):

The title compound was prepared (19 mg) according to the method presented in the synthesis of Example 54 utilizing **54B** and (2S,4R)-4-(benzyloxy)-1-(tert-butoxycarbonyl)pyrrolidine-2-carboxylic acid. ^1H NMR (400 MHz, CDCl_3) δ 9.08 (s, 1H), 8.75 (s, 1H), 7.94 (s, 1H), 7.85 – 7.71 (m, 1H), 7.64 (d, 4H), 7.33 – 7.23 (m, 11H), 7.23 – 7.21 (m, 1H), 7.08 (s, 1H), 6.59 (s, 1H), 6.33 (s, 1H), 6.28 (d, 3H), 5.54 (s, 1H), 4.47 (d, 3H), 4.32 (t, 2H), 4.11 (s, 1H), 3.78 (s, 1H), 3.67 (s, 1H), 3.58 (s, 1H), 3.20 (s, 1H), 3.09 (s, 1H), 2.36 (s, 1H), 1.90 (s, 1H), 1.41 (s, 8H), 1.23 (s, 4H).

Example 146



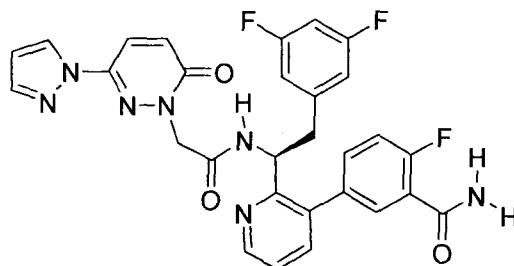
146

Synthesis of (S)-N-(1-(3-(4-chlorophenyl)pyridin-2-yl)-2-(3,5-difluorophenyl)ethyl)-2-(3-oxo-2,3,4,5,6,7-hexahydro-1H-indazol-1-yl)acetamide (**146**):

The title compound was prepared (14 mg) according to the method presented in the synthesis of Example 36 utilizing **36E** and **123D**. ^1H NMR (400 MHz, CD_3OD) δ 8.76 – 8.36 (m, 1H), 7.61 (dd, 1H), 7.50 – 7.25 (m, 1H), 7.09 (d, 1H), 6.70 (d, 1H), 6.29 (d, 1H), 5.40 (t, 1H), 5.10 (s, 1H),

4.84 (s, 8H), 4.72 – 4.54 (m, 1H), 3.29 (dt, 8H), 3.10 (d, 1H), 2.99 (d, 1H), 2.61 (s, 1H), 2.60 – 2.16 (m, 2H), 2.24 – 2.16 (m, 1H), 2.01 (s, 1H), 1.76 (d, 2H). MS (m/z) 523.9 $[M+H]^+$.

Example 147

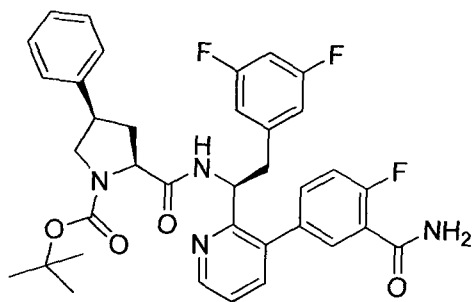


147

Synthesis of (S)-5-(2-(2-(3,5-difluorophenyl)-1-(2-(6-oxo-3-(1H-pyrazol-1-yl)pyridazin-1(6H)-yl)acetamido)ethyl)pyridin-3-yl)-2-fluorobenzamide (**147**):

The title compound was prepared (21 mg) according to the method presented in the synthesis of Example 54 utilizing **54B** and 2-(6-oxo-3-(1H-pyrazol-1-yl)pyridazin-1(6H)-yl)acetic acid. ^1H NMR (400 MHz, dmso) δ 8.94 (d, 1H), 8.71 – 8.64 (m, 1H), 8.15 (d, 1H), 8.02 (d, 1H), 7.80 (d, 1H), 7.71 – 7.55 (m, 3H), 7.47 – 7.36 (m, 3H), 7.34 – 7.20 (m, 1H), 7.11 (d, 1H), 6.89 (t, 1H), 6.60 – 6.42 (m, 3H), 5.16 (d, 1H), 4.63 (q, 2H), 3.00 (d, 2H), 2.52 – 2.41 (m). MS (m/z) 574.3 $[M+H]^+$.

Example 148



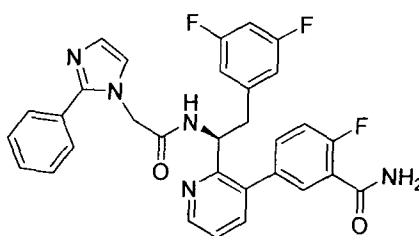
148

Synthesis of (2S,4R)-tert-butyl 2-((S)-1-(3-(3-carbamoyl-4-fluorophenyl)pyridin-2-yl)-2-(3,5-difluorophenyl)ethylcarbamoyl)-4-phenylpyrrolidine-1-carboxylate (**148**):

The title compound was prepared (16 mg) according to the method presented in the synthesis of Example 54 utilizing **54B** and (2S,4R)-1-(tert-butoxycarbonyl)-4-phenylpyrrolidine-2-carboxylic acid. ^1H NMR (400 MHz, cdcl_3) δ 9.06 (s, 1H), 8.76 (s, 1H), 7.98 (s, 1H), 7.72 (s, 2H), 7.63 (s, 1H), 7.44 – 7.14 (m, 3H), 6.58 (s, 1H), 6.27 (d, $J = 22.0$ Hz, 3H), 5.64 (s, 1H), 4.40

(s, 1H), 4.01 (s, 1H), 3.32 (s, 3H), 3.21 (s, 2H), 2.25 (s, 3H), 1.45 (s, 7H), 1.28 (s, 3H). MS (m/z) 645.1 $[M+H]^+$.

Example 149

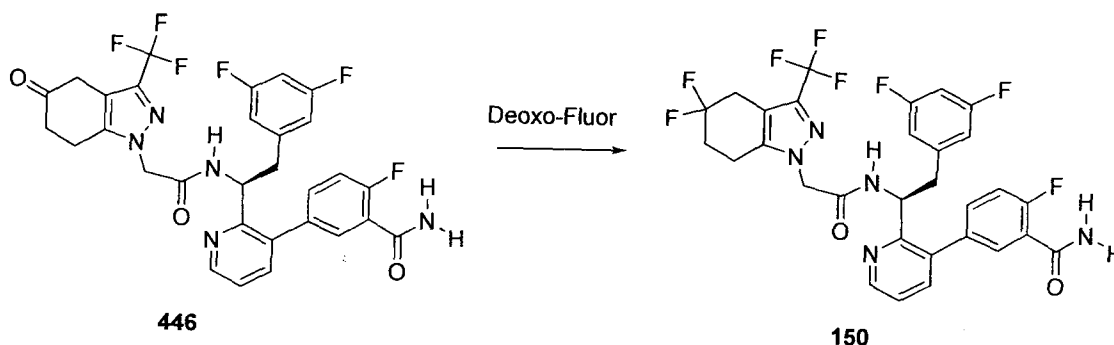


149

Synthesis of (S)-5-(2-(2-(3,5-difluorophenyl)-1-(2-(2-phenyl-1H-imidazol-1-yl)acetamido)ethyl)pyridin-3-yl)-2-fluorobenzamide (**149**):

The title compound was prepared (7 mg) according to the method presented in the synthesis of Example 54 utilizing **54B** and 2-(2-phenyl-1H-imidazol-1-yl)acetic acid. ^1H NMR (400 MHz, dmso) δ 9.13 (d, 1H), 8.69 (d, 1H), 7.74 (s, 1H), 7.72 – 7.49 (m, 6H), 7.50 (s, 1H), 7.56 – 7.39 (m, 6H), 7.31 (d, 2H), 6.95 (s, 1H), 6.51 (d, 2H), 5.11 (d, 1H), 4.85 (s, 3H), 2.95 (dd, 2H), 2.52 – 2.41 (m, 38H). MS (m/z) 556.6 $[M+H]^+$.

Example 150



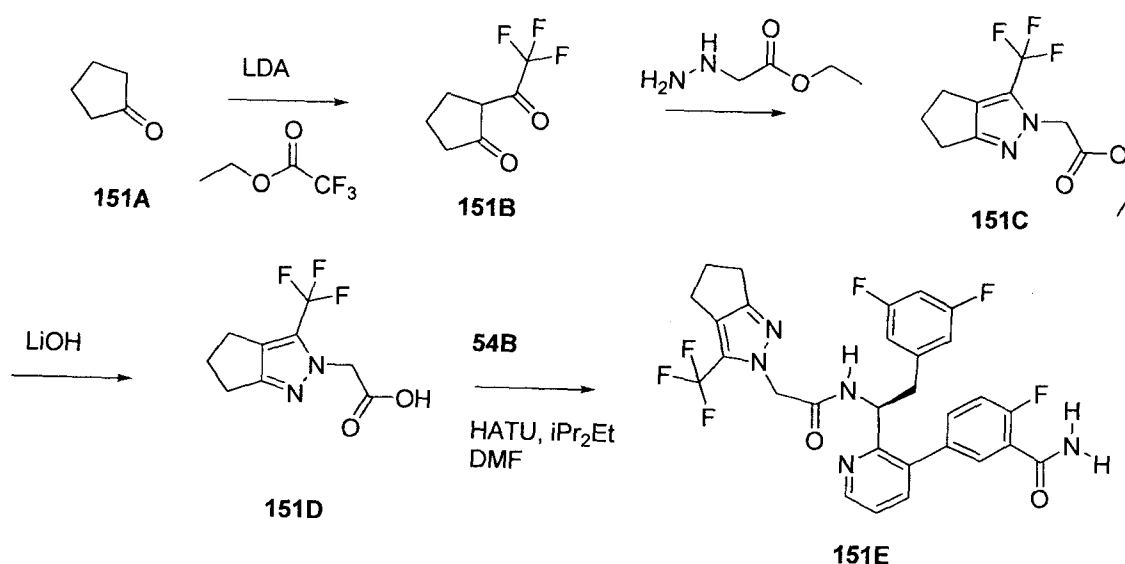
446

150

Synthesis of (S)-5-(2-(1-(2-(5,5-difluoro-3-(trifluoromethyl)-4,5,6,7-tetrahydro-1H-indazol-1-yl)acetamido)-2-(3,5-difluorophenyl)ethyl)pyridin-3-yl)-2-fluorobenzamide (**150**)

In a plastic bottle, **446** (15 mg, 0.024 mmol) was dissolved in DCM (0.10 mL) and treated with Deoxo-Fluor (25 μL). After 15 min at ambient temperature, the reaction was quenched with aqueous saturated NaHCO_3 and extracted with DCM. The organics evaporated and the residue was purified by RP HPLC to provide the desired compound (3 mg). ^{19}F NMR (376 MHz, cdCl_3) δ -62.32, -76.30, -98.50, -109.31. MS (m/z) 638.2 $[M+H]^+$.

Example 151



Synthesis of 2-(2,2,2-trifluoroacetyl)cyclopentanone (**151B**):

The title compound was prepared according to the method presented in the synthesis of **122C** in Example 122 utilizing cyclopentanone.

Synthesis of ethyl 2-(3-(trifluoromethyl)-5,6-dihydrocyclopenta[c]pyrazol-2(4H)-yl)acetate (**151C**):

The title compound was prepared according to the method presented in the synthesis of **122D** in Example 122 utilizing 2-(2,2,2-trifluoroacetyl)cyclopentanone. The title compound was the exclusive product of this reaction. MS (m/z) 263.1 $[\text{M}+\text{H}]^+$.

Synthesis of 2-(3-(trifluoromethyl)-5,6-dihydrocyclopenta[c]pyrazol-2(4H)-yl)acetic acid (**151D**):

The title compound was prepared according to the method presented in the synthesis of **122F** in Example 122 utilizing ethyl 2-(3-(trifluoromethyl)-5,6-dihydrocyclopenta[c]pyrazol-2(4H)-yl)acetate. MS (m/z) 235.0 $[\text{M}+\text{H}]^+$.

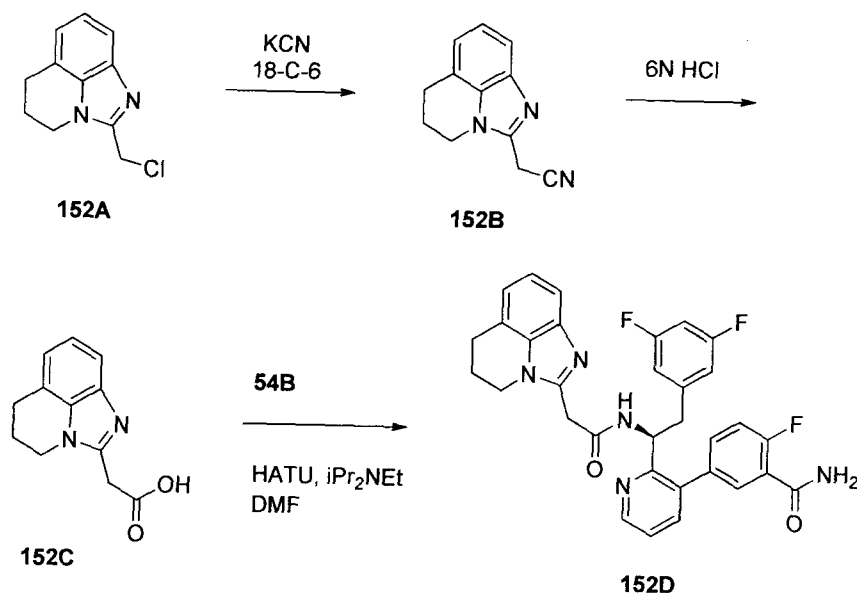
Synthesis of (S)-5-(2-(2-(3,5-difluorophenyl)-1-(2-(3-(trifluoromethyl)-5,6-dihydrocyclopenta[c]pyrazol-2(4H)-yl)acetamido)ethyl)pyridin-3-yl)-2-fluorobenzamide (**151E**):

The title compound was prepared (8 mg) according to the method presented in the synthesis of Example 54 utilizing **54B** and **151D**. ^1H NMR (400 MHz, dmso) δ 8.79 (d, 1H), 8.67 (d, 1H),

7.73 – 7.57 (m, 3H), 7.40 (dt, 3H), 7.30 (s, 1H), 6.91 (s, 1H), 6.54 (d, 2H), 5.14 (s, 1H), 4.72 (s, 2H), 2.98 (s, 2H), 2.63 – 2.52 (m, 4H), 2.52 – 2.41 (m), 2.30 (s, 2H). MS (m/z) 588.3 $[M+H]^+$.

Example 152

5



Synthesis of 2-(5,6-dihydro-4H-imidazo[4,5,1-ij]quinolin-2-yl)acetonitrile (**152B**):

To 2-(chloromethyl)-5,6-dihydro-4H-imidazo[4,5,1-ij]quinoline (synthesized as described in US 2007/0032469) (700 mg, 3.39 mmol) dissolved in EtOH (12 mL)/H₂O (1.2 mL) was added 18-C-6 (catalytic amount) and KCN (220 mg, 3.39 mmol). The reaction was heated to 50 °C for 3 h. Solvents were removed in vacuo and the residue was purified by column chromatography on silica to provide the title compound. MS (m/z) 198.1 $[M+H]^+$.

Synthesis of 2-(5,6-dihydro-4H-imidazo[4,5,1-ij]quinolin-2-yl)acetic acid (**152C**):

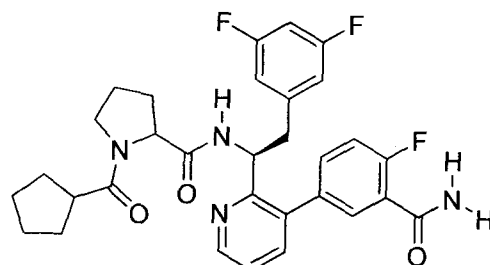
2-(5,6-dihydro-4H-imidazo[4,5,1-ij]quinolin-2-yl)acetonitrile (90 mg, 0.45 mmol) was dissolved in 6 N HCl (3 mL) and heated to 70 °C. After 1 h, the reaction temperature was raised to 105 °C. After 2 h, the reaction was cooled to 0 °C, neutralized with 20% aqueous NaOH, and buffered with 20% aqueous KH₂PO₄. The product was water soluble and unable to extract into organic solvents. The aqueous solution was removed in vacuo and crude product was directly used in the next reaction. MS (m/z) 217.1 $[M+H]^+$.

Synthesis of (S)-5-(2-(2-(3,5-difluorophenyl)-1-(2-(5,6-dihydro-4H-imidazo[4,5,1-ij]quinolin-2-yl)acetamido)ethyl)pyridin-3-yl)-2-fluorobenzamide (**152D**):

The title compound (4 mg) was prepared according to the method presented in the synthesis of Example 54G utilizing **54B** and 2-(5,6-dihydro-4H-imidazo[4,5,1-ij]quinolin-2-yl)acetic acid.

¹H NMR (400 MHz, cd₃od) δ 8.60 (d, 1H), 7.52 – 7.45 (m, 1H), 7.37 (d, 1H), 7.31 – 7.23 (m, 1H), 7.21 (s, 1H), 7.15 – 6.98 (m, 2H), 6.91 (d, 1H), 6.54 (t, 1H), 6.26 (d, 2H), 5.28 (t, 1H), 4.75 (s, 19H), 3.98 (s, 2H), 3.83 (s, 1H), 3.24 (s, 1H), 3.38 – 2.92 (m, 23H), 2.86 (t, 2H), 2.30 – 1.90 (m, 2H). MS (*m/z*) 570.4 [M+H]⁺.

Example 153

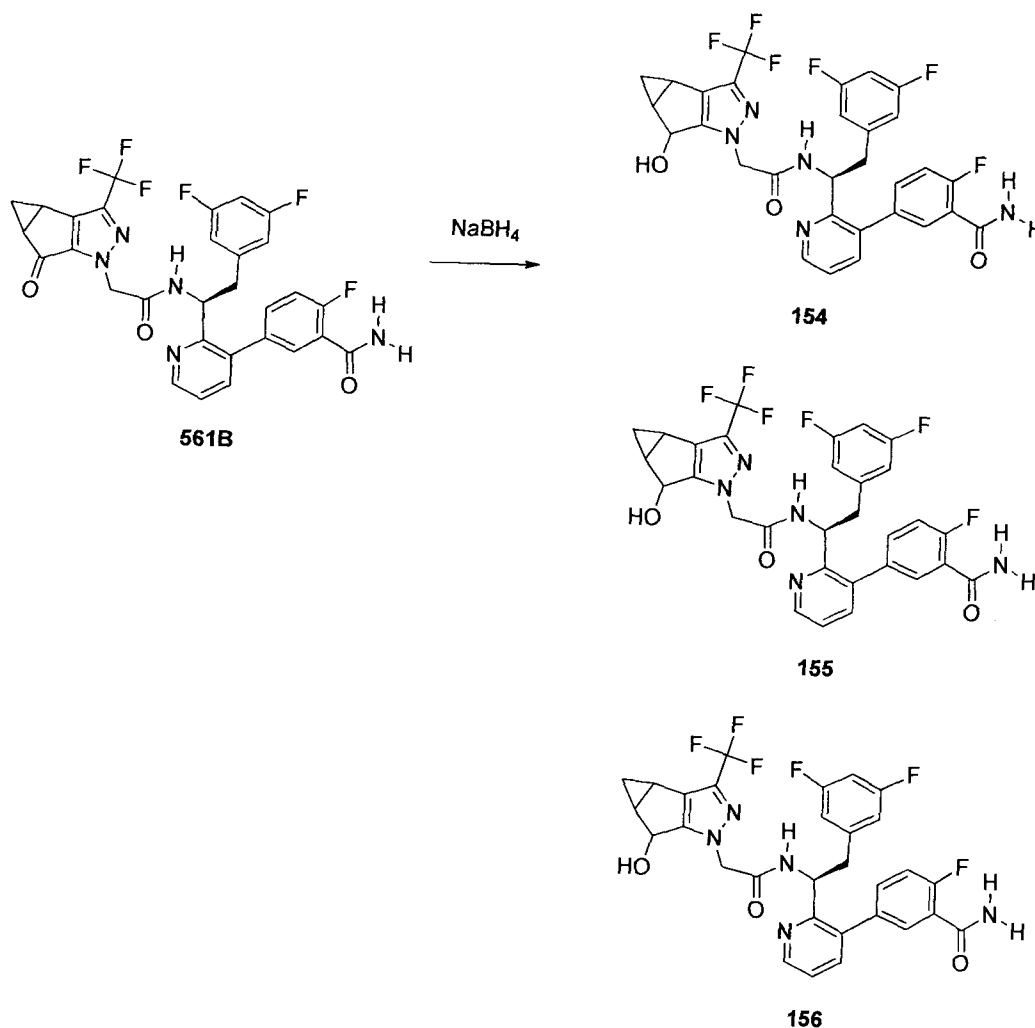


153

10 Synthesis of N-((S)-1-(3-(3-carbamoyl-4-fluorophenyl)pyridin-2-yl)-2-(3,5-difluorophenyl)ethyl)-1-(cyclopentanecarbonyl)pyrrolidine-2-carboxamide (**153**):

The title compound was prepared (6 mg) according to the method presented in the synthesis of Example 54 utilizing **54B** and 1-(cyclopentanecarbonyl)pyrrolidine-2-carboxylic acid. ¹H NMR (400 MHz, cdcl₃) δ 8.78 (s, 1H), 8.71 (s, 1H), 8.02 (s, 1H), 7.75 (s, 2H), 7.61 (s, 1H), 7.31 (s, 1H), 6.59 (s, 1H), 6.28 (d, *J* = 6.2 Hz, 2H), 6.06 (s, 1H), 5.61 (s, 1H), 4.33 (s, 1H), 3.95 (s, 1H), 3.55 (s, 1H), 3.28 (d, *J* = 28.6 Hz, 2H), 3.03 (s, 1H), 2.13 (s, 6H), 1.93 (s, 6H), 1.61 (d, *J* = 43.1 Hz, 6H).

Example 154, 155, and 156



Synthesis of 5-(2-((1S)-2-(3,5-difluorophenyl)-1-(2-(5-hydroxy-3-(trifluoromethyl)-3b,4,4a,5-tetrahydro-1H-cyclopropa[3,4]cyclopenta[1,2-c]pyrazol-1-yl)acetamido)ethyl)pyridin-3-yl)-2-fluorobenzamide (**154**):

- 5 The title compound was prepared according to the method presented in the synthesis of **325B** in Example 325 utilizing **561B**. Purification of the crude mixture by RP HPLC resulted in isolation of three peaks. Compound 154 (3.5 mg) is the peak with the shortest retention time. ¹H NMR (400 MHz, cd₃cn) δ 8.58 (dd, 1H), 8.17 (s, 1H), 7.70 (dd, 1H), 7.65 – 7.43 (m, 2H), 7.26 (s, 1H), 7.17 (dd, 1H), 6.77 (s, 1H), 6.61 (t, 1H), 6.27 (t, 3H), 5.34 – 5.21 (m, 2H), 4.61 (q, 2H), 3.32 (s, 2H), 2.94 (qd, 3H), 2.30 – 1.90 (m, 3H), 1.85 (dt), 0.89 (td, 1H), 0.72 (dd, 1H). MS (*m/z*) 616.1 [M+H]⁺.

15 Synthesis of 5-(2-((1S)-2-(3,5-difluorophenyl)-1-(2-(5-hydroxy-3-(trifluoromethyl)-3b,4,4a,5-tetrahydro-1H-cyclopropa[3,4]cyclopenta[1,2-c]pyrazol-1-yl)acetamido)ethyl)pyridin-3-yl)-2-fluorobenzamide (**155**):

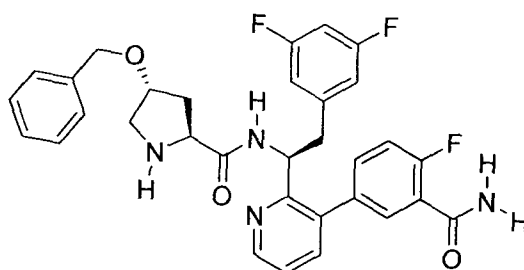
The title compound was prepared according to the method presented in the synthesis of **325B** in Example 325 utilizing **561B**. Purification of the crude mixture by RP HPLC resulted in isolation of three peaks. Compound 155 (5 mg) is the peak with second shortest retention time and is a mixture of diastereomers. ¹H NMR (400 MHz, cd₃cn) δ 8.57 – 8.45 (m, 1H), 7.68 (dd, 1H), 7.66 – 7.41 (m, 2H), 7.41 – 7.06 (m, 3H), 7.06 – 7.03 (m, 1H), 6.61 (d, 2H), 6.50 (d, 1H), 6.33 – 5.90 (m, 4H), 5.27 – 5.06 (m, 2H), 4.64 – 4.47 (m, 2H), 3.62 (s, 6H), 3.17 – 2.66 (m, 3H), 1.96 (ddd, 3H), 1.75 (dt), 1.09 – 0.87 (m, 1H), 0.78 (dd, 1H), 0.61 (d, 1H), 0.02 (dd, *J* = 8.3, 4.7 Hz, 1H). MS (*m/z*) 616.1 [M+H]⁺.

- 10 Synthesis of 5-(2-((1S)-2-(3,5-difluorophenyl)-1-(2-(5-hydroxy-3-(trifluoromethyl)-3b,4,4a,5-tetrahydro-1H-cyclopropa[3,4]cyclopenta[1,2-c]pyrazol-1-yl)acetamido)ethyl)pyridin-3-yl)-2-fluorobenzamide (**156**):

The title compound was prepared according to the method presented in the synthesis of **325B** in Example 325 utilizing **561B**. Purification of the crude mixture by RP HPLC resulted in isolation of three peaks. Compound 156 (4 mg) is the peak with longest retention time and is a mixture of diastereomers. ¹H NMR (400 MHz, cd₃cn) δ 8.68 (d, 1H), 7.73 (s, 1H), 7.63 (s, 1H), 7.51 (s, 1H), 7.36 – 7.23 (m, 2H), 6.90 (s, 1H), 6.69 (s, 1H), 6.34 (d, 4H), 5.34 (d, 2H), 4.74 (dd, 2H), 3.00 (d, 3H), 2.16 (s, 1H), 1.95 (dt), 1.20 (s, 1H), 0.97 (d, 1H), 0.75 (d, 1H), 0.22 (s, 1H). MS (*m/z*) 616.1 [M+H].

20

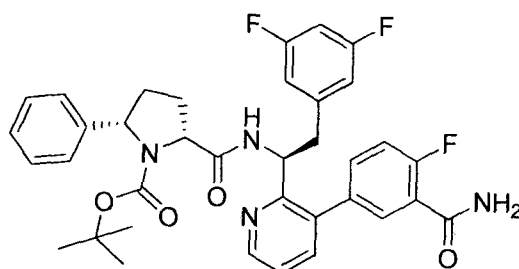
Example 157

**157**

Synthesis of (2S,4R)-4-(benzyloxy)-N-((S)-1-(3-(3-carbamoyl-4-fluorophenyl)pyridin-2-yl)-2-(3,5-difluorophenyl)ethyl)pyrrolidine-2-carboxamide (**157**):

- 25 The title compound was prepared (9 mg) according to the method presented in the synthesis of Example 125 utilizing **145**. MS (*m/z*) 575.4 [M+H]⁺.

Example 158

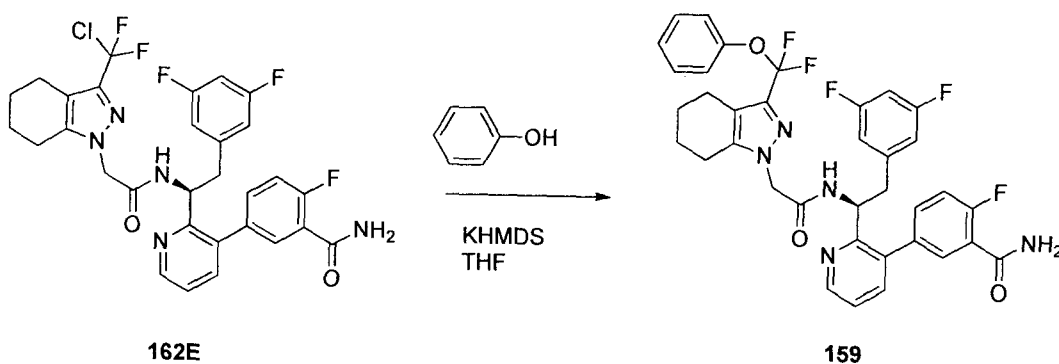
**158**

Synthesis of (2R,5S)-tert-butyl 2-((S)-1-(3-(3-carbamoyl-4-fluorophenyl)pyridin-2-yl)-2-(3,5-difluorophenyl)ethylcarbamoyl)-5-phenylpyrrolidine-1-carboxylate (**158**):

The title compound was prepared (6 mg) according to the method presented in the synthesis of Example 54 utilizing **54B** and (2R,5S)-1-(tert-butoxycarbonyl)-5-phenylpyrrolidine-2-carboxylic acid. ¹H NMR (400 MHz, cdcl₃) δ 8.74 (d, 1H), 8.6 (m, 1H) 7.86 (s, 1H), 7.62 (d, 2H), 7.33 – 7.22 (m, 10H), 6.59 (s, 1H), 6.19 (d, 2H), 6.06 (s, 1H), 5.48 (s, 1H), 4.59 (d, 1H), 3.11 (s, 1H), 3.02 (s, 1H), 2.53 (s, 2H), 2.43 (s, 2H), 1.86 (s, 1H), 1.41 (s, 10H). MS (*m/z*) 645.1 [M+H]⁺.

10

Example 159

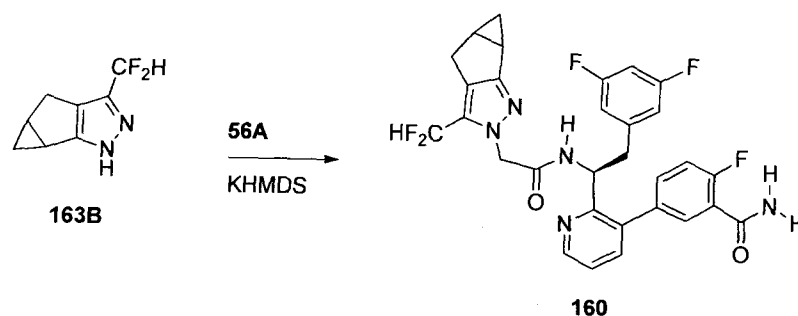
**162E****159**

Synthesis of (S)-5-(2-(1-(2-(3-(difluoro(phenoxy)methyl)-4,5,6,7-tetrahydro-1H-indazol-1-yl)acetamido)-2-(3,5-difluorophenyl)ethyl)pyridin-3-yl)-2-fluorobenzamide (**159**):

(S)-5-(2-(1-(2-(3-(chlorodifluoromethyl)-4,5,6,7-tetrahydro-1H-indazol-1-yl)acetamido)-2-(3,5-difluorophenyl)ethyl)pyridin-3-yl)-2-fluorobenzamide (36 mg, 0.06 mmol) was dissolved in THF (0.6 mL) and treated with KHMDS (2.7 mg, 0.14 mmol). Phenol (14 mg, 0.15 mmol) was added to the reaction mixture the temperature was raised to 45 °C. After stirring for 16 h, solvent were removed in vacuo. The residue was purified by RP HPLC to provide the title compound (7 mg) as a mixture with its regioisomer ((S)-5-(2-(1-(2-(3-(difluoro(phenoxy)methyl)-4,5,6,7-tetrahydro-2H-indazol-2-yl)acetamido)-2-(3,5-difluorophenyl)ethyl)pyridin-3-yl)-2-fluorobenzamide : ¹H NMR (400 MHz, dmso) δ 8.88 (d, 1H), 8.81 – 8.59 (m, 2H), 7.84 – 7.55

(m, 4H), 7.55 – 7.14 (m, 8H), 7.10 (d, 1H), 7.05 – 6.81 (m, 1H), 6.56 (d, 2H), 6.47 (d, 1H), 5.22 – 5.12 (m, 1H), 4.84 (s, 2H), 4.74 (d, 16H), 3.18 – 2.72 (m, 3H), 2.52 – 2.42 (m, 12H), 2.25 (d, 1H), 1.60 (s, 6H). MS (*m/z*) 676.2 [*M*+H]⁺.

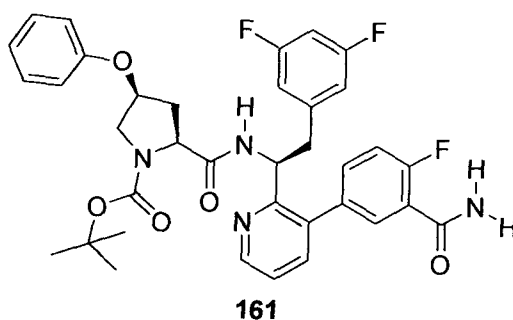
5 Example 160



Synthesis of 5-(2-(((1S)-1-(2-(3-(difluoromethyl)-4,4a,5,5a-tetrahydro-2H-cyclopropa[4,5]cyclopenta[1,2-c]pyrazol-2-yl)acetamido)-2-(3,5-difluorophenyl)ethyl)pyridin-3-yl)-2-fluorobenzamide (**160**):

- 10 The title compound was prepared (8 mg) according to the method presented in the synthesis of Example 56 utilizing **56A** and **163B** to provide to regioisomeric products. The title compound was the minor product (8 mg): ¹H NMR (400 MHz, dmso) δ 8.63 (t, 1H), 8.53 (d, 1H), 7.47 (dd, 3H), 7.41 – 7.19 (m, 3H), 7.19 – 7.09 (m, 1H), 6.85 (s, 1H), 6.80 – 6.69 (m, 1H), 6.58 (d, 1H), 6.36 (d, 2H), 5.00 (d, 1H), 4.55 (s, 2H), 2.84 (t, 2H), 2.62 (d, 2H), 2.44 (d, 1H), 2.34 (s, 3H),
- 15 2.34 – 1.72 (m), 0.93 (d, 1H), 0.00 (d, *J* = 4.0 Hz, 2H). MS (*m/z*) 582.2 [*M*+H]⁺.

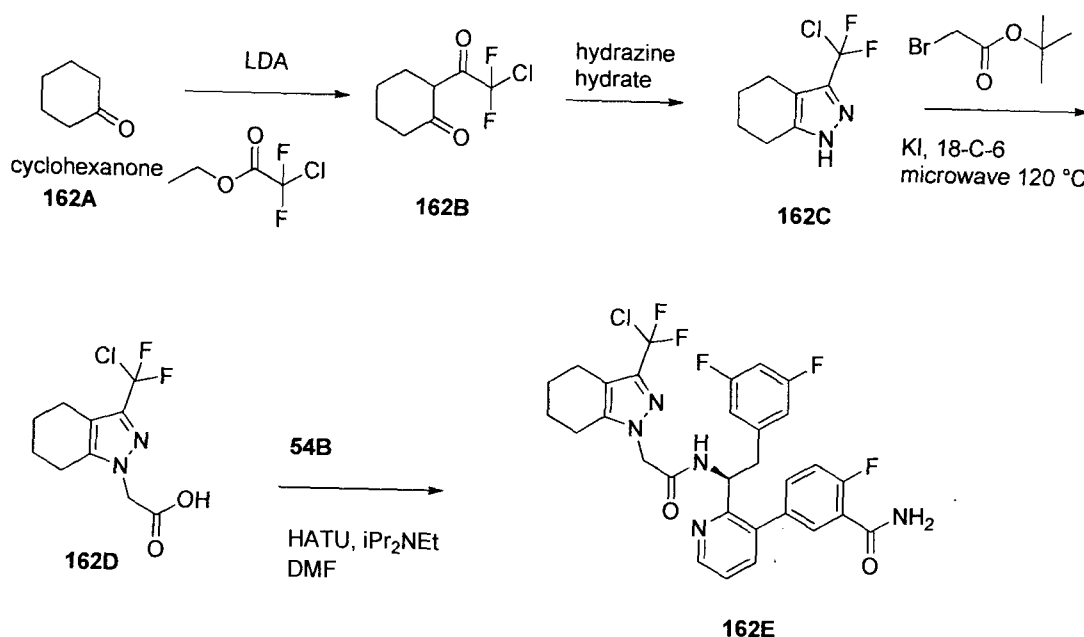
Example 161



- 20 Synthesis of (2S,4S)-tert-butyl 2-(((S)-1-(3-(3-carbamoyl-4-fluorophenyl)pyridin-2-yl)-2-(3,5-difluorophenyl)ethyl)carbamoyl)-4-phenoxyproline-1-carboxylate (**161**):

The title compound as prepared (12 mg) according to the method presented in the synthesis of Example 54 utilizing **54B** and (2S,4S)-1-(tert-butoxycarbonyl)-4-phenoxyproline-2-carboxylic acid. MS (*m/z*) 661.3 [*M*+H]⁺.

Example 162



Synthesis of 2-(2-chloro-2,2-difluoroacetyl)cyclohexanone (**162B**):

The title compound was prepared according to the method presented in the synthesis of **122C** in Example 122 utilizing cyclohexanone and ethyl 2-chloro-2,2-difluoroacetate.

Synthesis of 3-(chlorodifluoromethyl)-4,5,6,7-tetrahydro-1H-indazole (**162C**):

The title compound was prepared according to the method presented in the synthesis of **169D** in Example 169 utilizing 2-(2-chloro-2,2-difluoroacetyl)cyclohexanone. MS (m/z) 207.4 $[\text{M}+\text{H}]^+$.

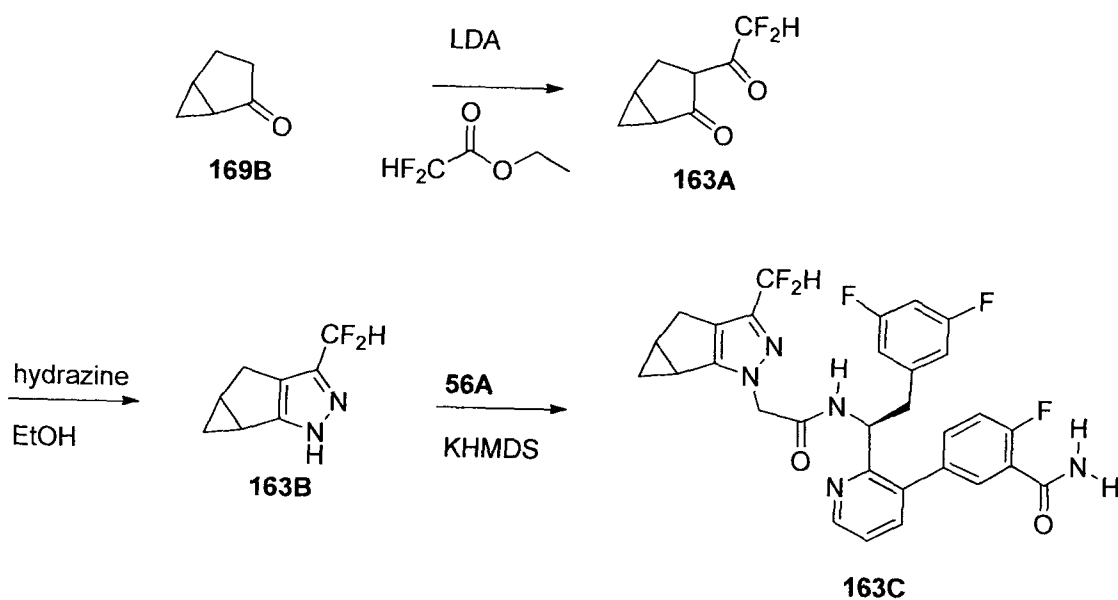
Synthesis of 2-(3-(chlorodifluoromethyl)-4,5,6,7-tetrahydro-1H-indazol-1-yl)acetic acid (**162D**):

In a microwave vial, 3-(chlorodifluoromethyl)-4,5,6,7-tetrahydro-1H-indazole (580 mg, 2.81 mmol) was combined with tert-butyl 2-bromoacetate (2.5 mL, 17 mmol), KI (166 mg), and 18-C-6 (catalytic) in NMP (2.8 mL). The reaction mixture was heated in a microwave reactor at 120 °C for 90 min. The reaction was partitioned between EtOAc and saturated aqueous NaCl. The organics were separated, dried and removed in vacuo. The residue was purified by column chromatography on silica to provide the title compound as a 1.5:1 mixture with its regioisomer 2-(3-(chlorodifluoromethyl)-4,5,6,7-tetrahydro-2H-indazol-2-yl)acetic acid. MS (m/z) 265.1 $[\text{M}+\text{H}]^+$.

Synthesis of (S)-5-(2-(1-(2-(3-(chlorodifluoromethyl)-4,5,6,7-tetrahydro-1H-indazol-1-yl)acetamido)-2-(3,5-difluorophenyl)ethyl)pyridin-3-yl)-2-fluorobenzamide (**162E**):

The title compound was prepared according to the method presented in the synthesis of Example 54 utilizing **162D**. The title compound (5 mg) was not able to be purified from the regioisomer ((S)-5-(2-(1-(2-(3-(chlorodifluoromethyl)-4,5,6,7-tetrahydro-2H-indazol-2-yl)acetamido)-2-(3,5-difluorophenyl)ethyl)pyridin-3-yl)-2-fluorobenzamide) and was tested as a mixture. ¹H NMR (400 MHz, cd₃od) δ 8.68 (s, 1H), 7.60 (s, 1H), 7.36 (d, *J* = 22.1 Hz, 3H), 7.21 (s, 1H), 6.66 (s, 1H), 6.32 (s, 2H), 5.36 (s, 2H), 3.03 (s, 2H), 2.62 (s, 3H), 2.44 (s, 2H), 1.76 (s, 4H). MS (*m/z*) 618.7 [M+H]⁺.

Example 163



Synthesis of 3-(2,2-difluoroacetyl)bicyclo[3.1.0]hexan-2-one (**163A**):

The title compound was prepared according to the method presented in the synthesis of **122C** in Example 122 utilizing **169B** and ethyl 2,2-difluoroacetate.

15 Synthesis of 3-(difluoromethyl)-4,4a,5,5a-tetrahydro-1H-cyclopropa[4,5]cyclopenta[1,2-c]pyrazole (**163B**):

The title compound was prepared according to the method presented in the synthesis of **169D** in Example 169 utilizing **163A**. MS (*m/z*) 171.0 [M+H]⁺.

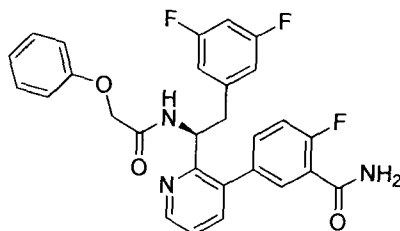
20 Synthesis of 5-(2-((1S)-1-(2-(3-(difluoromethyl)-4,4a,5,5a-tetrahydro-1H-cyclopropa[4,5]cyclopenta[1,2-c]pyrazol-1-yl)acetamido)-2-(3,5-difluorophenyl)ethyl)pyridin-3-yl)-2-fluorobenzamide (**163C**):

The title compound was prepared according to the method presented in the synthesis of Example 56 utilizing **56A** and **163B** to provide to regioisomeric products. The title compound was the

major product (6 mg): ^1H NMR (400 MHz, dmso) δ 8.67 (d, 1H), 8.47 (d, 1H), 7.57 – 7.35 (m, 3H), 7.35 – 7.16 (m, 3H), 7.16 – 7.01 (m, 1H), 6.69 (dd, 2H), 6.48 (s, 1H), 6.35 (d, 3H), 5.23 – 4.92 (m, 2H), 4.74 – 4.39 (m, 4H), 3.90 (s, 1H), 2.80 (d, 3H), 2.65 – 2.33 (m, 3H), 2.32 (s, 1H), 2.30 – 2.22 (m), 1.81 (d, 5H), 0.77 (dd, 2H), 0.00 (d, 1H). MS (m/z) 582.2 $[\text{M}+\text{H}]^+$.

5

Example 164

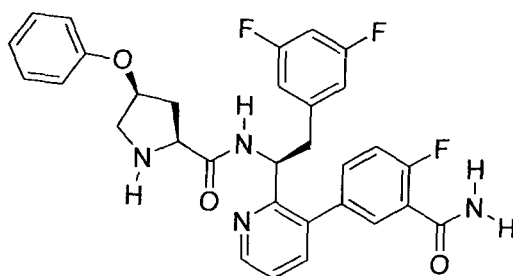


164

Synthesis of (S)-5-(2-(2-(3,5-difluorophenyl)-1-(2-phenoxyacetamido)ethyl)pyridin-3-yl)-2-fluorobenzamide (**164**):

10 Under the conditions described in Example 159, the title compound was isolated as side product (2 mg): ^1H NMR (400 MHz, dmso) δ 8.66 (dd, 1H), 8.57 (d, 1H), 7.87 – 7.58 (m, 4H), 7.54 (s, 1H), 7.54 – 7.28 (m, 4H), 7.28 – 7.15 (m, 2H), 6.90 (dd, 2H), 6.78 (d, 2H), 6.55 (d, 2H), 5.21 (d, 2H), 4.41 (s, 3H), 3.79 (bs), 3.17 – 2.90 (m, 3H), 2.52 – 2.41 (m, 14H). MS (m/z) 506.4 $[\text{M}+\text{H}]^+$.

15 Example 165

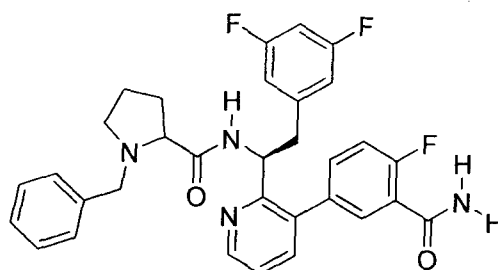


165

Synthesis of (2S,4S)-N-((S)-1-(3-(3-carbamoyl-4-fluorophenyl)pyridin-2-yl)-2-(3,5-difluorophenyl)ethyl)-4-phenoxyproline-2-carboxamide (**165**):

The title compound was prepared (3 mg) according to the method presented in the synthesis of
20 Example 125 utilizing **161**.

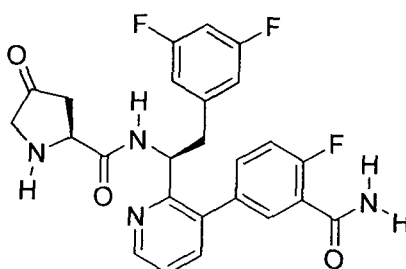
Example 166

**166**

Synthesis of 1-benzyl-N-((S)-1-(3-(3-carbamoyl-4-fluorophenyl)pyridin-2-yl)-2-(3,5-difluorophenyl)ethyl)pyrrolidine-2-carboxamide (**166**):

The title compound was prepared (31 mg) according to the method presented in the synthesis of Example 54 utilizing **54B** and 1-benzylpyrrolidine-2-carboxylic acid. MS (*m/z*) 559.4 [*M*+*H*]⁺.

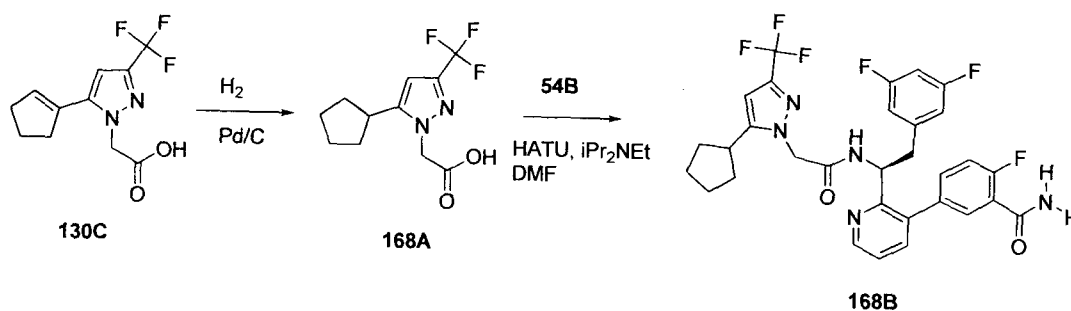
Example 167

**167**

Synthesis of (S)-N-((S)-1-(3-(3-carbamoyl-4-fluorophenyl)pyridin-2-yl)-2-(3,5-difluorophenyl)ethyl)-4-oxopyrrolidine-2-carboxamide (**167**):

The title compound was prepared (5 mg) according to the method presented in the synthesis of Example 125 utilizing **137**. MS (*m/z*) 483.4 [*M*+*H*]⁺.

Example 168



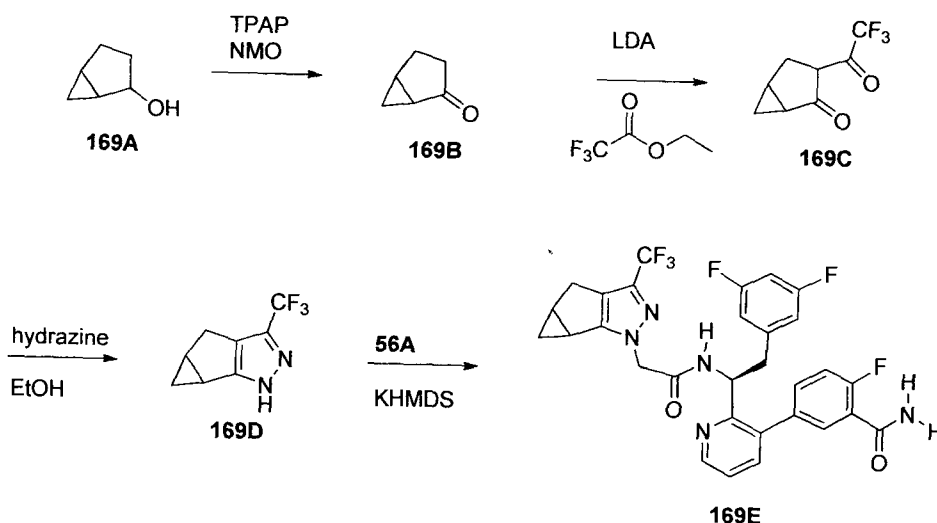
Synthesis of 2-(5-cyclopentyl-3-(trifluoromethyl)-1H-pyrazol-1-yl)acetic acid (**168A**):

To **130C** (30 mg, 0.11 mmol) dissolved in EtOH (4 mL) was added Pd/C (5 mg) and placed under an atmosphere of H₂. The reaction was stirred for 16 h then filtered over celite. The eluent was removed in vacuo. MS (*m/z*) 263.1 [M+H]⁺.

- 5 Synthesis of (S)-5-(2-(1-(2-(5-cyclopentyl-3-(trifluoromethyl)-1H-pyrazol-1-yl)acetamido)-2-(3,5-difluorophenyl)ethyl)pyridin-3-yl)-2-fluorobenzamide (**168B**):

The title compound was prepared (5 mg) according to the method presented in the synthesis of Example 54 utilizing **54B** and **168A**. ¹H NMR (400 MHz, dmso) δ 8.92 (d, 1H), 8.67 (d, 1H), 7.67 – 7.58 (m, 3H), 7.53 – 7.31 (m, 4H), 7.29 (d, 1H), 6.92 (s, 1H), 6.57 (d, 2H), 6.44 (s, 1H), 5.17 (d, 2H), 4.80 (q, 4H), 3.01 (t, 2H), 2.72 (t, 1H), 2.52 – 2.41 (m), 1.77 (s, 1H), 1.77 – 1.66 (m, 1H), 1.54 (d, 4H), 1.37 (d, 1H). MS (*m/z*) 616.4 [M+H]⁺.

Example 169



- 15 Synthesis of bicyclo[3.1.0]hexan-2-one (**169B**):

The title compound was prepared according to the method presented in the synthesis of **122B** in Example 122 utilizing bicyclo[3.1.0]hexan-2-ol (synthesized as described in *J. Am. Chem. Soc.* **2004**, 126, 8664-8665).

- 20 Synthesis of 3-(2,2,2-trifluoroacetyl)bicyclo[3.1.0]hexan-2-one (**169C**):

The title compound was prepared according to the method presented in the synthesis of **122C** in Example 122 utilizing bicyclo[3.1.0]hexan-2-one.

- 25 Synthesis of 3-(trifluoromethyl)-4,4a,5,5a-tetrahydro-1H-cyclopropa[4,5]cyclopenta[1,2-c]pyrazole (**169D**):

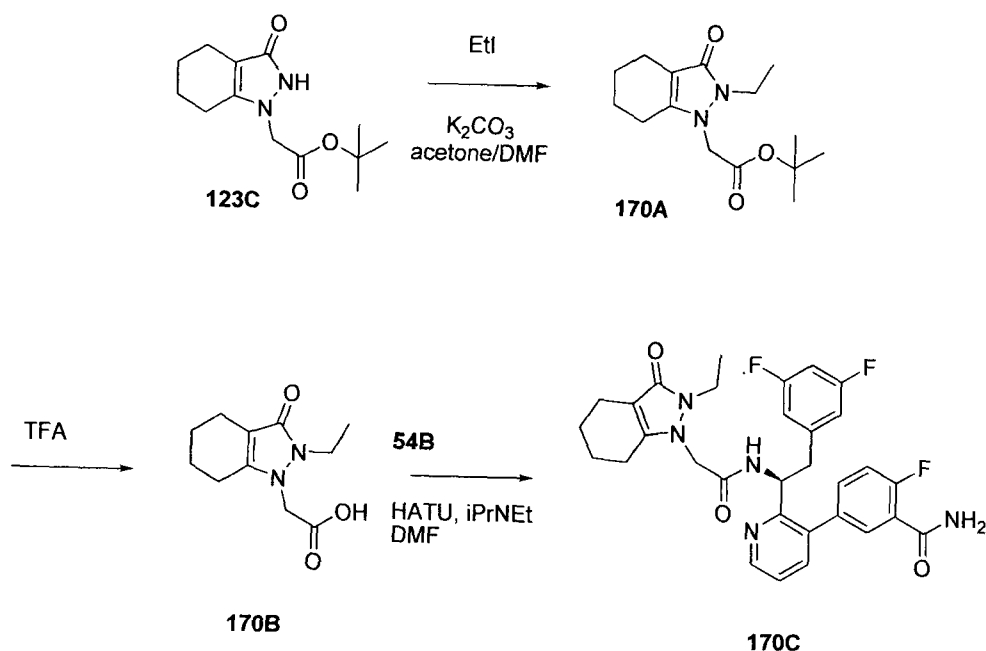
To 3-(2,2,2-trifluoroacetyl)bicyclo[3.1.0]hexan-2-one (290 mg, 1.5 mmol) dissolved in EtOH (14 mL) was added hydrazine hydrate (2 mmol) and heated to 85 °C. After 16 hours, the reaction was cooled to ambient temperature and solvents removed in vacuo. The residue was partitioned between EtOAc and H₂O. The organics were separated, dried and removed in vacuo.

5 The crude product was purified by column chromatography on silica to provide the title compound. MS (*m/z*) 189.0 [M+H]⁺.

Synthesis of 5-(2-((1S)-2-(3,5-difluorophenyl)-1-(2-(3-(trifluoromethyl)-4,4a,5,5a-tetrahydro-1H-cyclopropa[4,5]cyclopenta[1,2-c]pyrazol-1-yl)acetamido)ethyl)pyridin-3-yl)-2-fluorobenzamide (**169E**):

10 The title compound was prepared (14 mg) according to the method presented in the synthesis of Example 56 utilizing **56A** and **169D**. MS (*m/z*) 600.3 [M+H]⁺.

Example 170



15 Synthesis of tert-butyl 2-(2-ethyl-3-oxo-2,3,4,5,6,7-hexahydro-1H-indazol-1-yl)acetate (**170A**): tert-Butyl 2-(3-oxo-2,3,4,5,6,7-hexahydro-1H-indazol-1-yl)acetate (52 mg, 0.21 mmol) was dissolved in acetone (2 mL) and treated with EtI (18 μL, 0.23 mmol) and K₂CO₃ (34 mg, 0.23 mmol). DMF (1 mL) was added to aid solubility and the reaction was heated to 50 °C for 14 hr.

20 Two alkylation regioisomers were obtained. The title compound was the minor regioisomer exhibiting a longer retention time on HPLC: MS (*m/z*) 281.1 [M+H]⁺.

Synthesis of 2-(2-ethyl-3-oxo-2,3,4,5,6,7-hexahydro-1H-indazol-1-yl)acetic acid (**170B**):

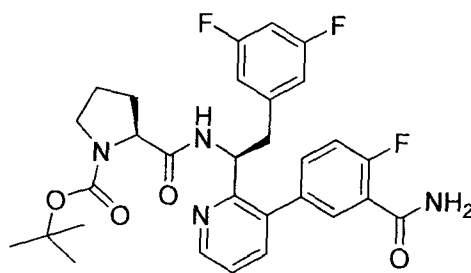
tert-Butyl 2-(2-ethyl-3-oxo-2,3,4,5,6,7-hexahydro-1H-indazol-1-yl)acetate (0.1 mmol) was dissolved in DCM (1 mL) and treated with TFA (1 mL). The reaction was stirred for 2 h at ambient temperature at which time solvents were removed in vacuo to provide the desired product: MS (m/z) 225.2 $[M+H]^+$.

5

Synthesis of (S)-5-(2-(2-(3,5-difluorophenyl)-1-(2-(2-ethyl-3-oxo-2,3,4,5,6,7-hexahydro-1H-indazol-1-yl)acetamido)ethyl)pyridin-3-yl)-2-fluorobenzamide (**170C**):

The title compound was prepared (14 mg) according to the method presented in the synthesis of Example 54 utilizing **54B** and 2-(2-ethyl-3-oxo-2,3,4,5,6,7-hexahydro-1H-indazol-1-yl)acetic acid. ^1H NMR (400 MHz, cd_3od) δ 8.73 – 8.66 (m, 1H), 7.63 – 7.55 (m, 1H), 7.50 (d, 1H), 7.32 (ddd, 3H), 6.69 (s, 1H), 6.37 (d, 2H), 5.31 (t, 1H), 4.83 (s, 20H), 4.72 – 4.58 (m, 3H), 4.12 (d, 1H), 4.01 – 3.67 (m, 3H), 3.29 (dt, 29H), 3.04 (t, 4H), 2.79 (s, 1H), 2.45 (d, 2H), 2.35 (d, 4H), 1.78 (s, 3H), 1.71 (s, 3H), 1.31 (t, 1H), 1.12 (t, 3H). MS (m/z) 578.5 $[M+H]^+$.

15 Example 171

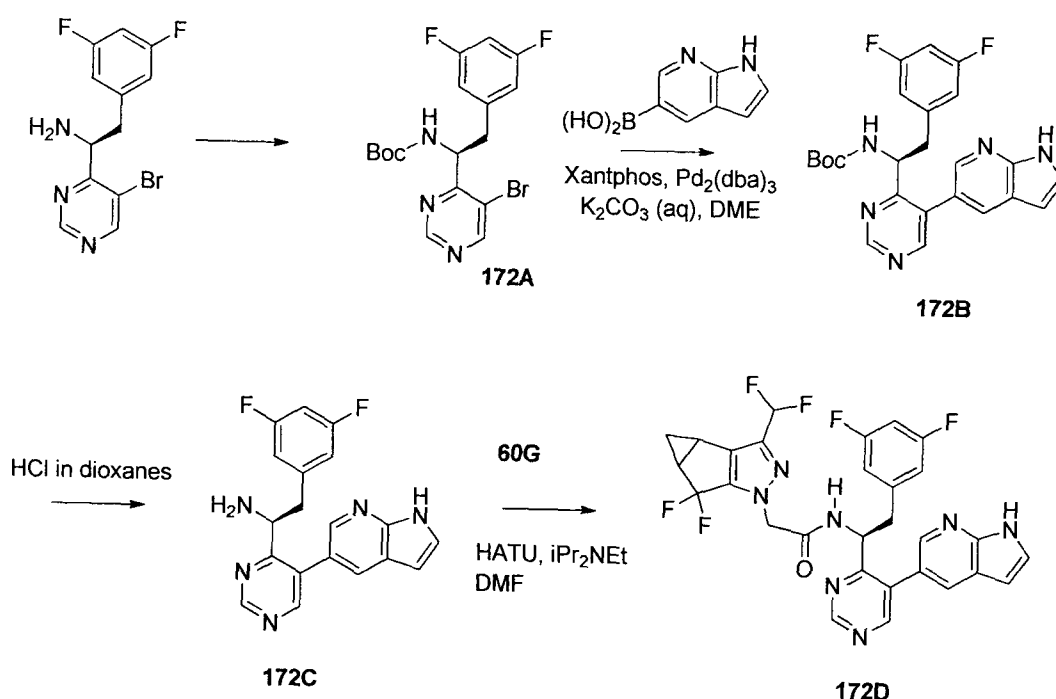


171

Synthesis of (S)-tert-butyl 2-((S)-1-(3-(3-carbamoyl-4-fluorophenyl)pyridin-2-yl)-2-(3,5-difluorophenyl)ethylcarbamoyl)pyrrolidine-1-carboxylate (**171**):

The title compound was prepared (6 mg) according to the method presented in the synthesis of Example 54 utilizing **54B** and (S)-1-(tert-butoxycarbonyl)pyrrolidine-2-carboxylic acid. MS (m/z) 569.2 $[M+H]^+$.

Example 172



Synthesis of (S)-tert-butyl 1-(5-bromopyrimidin-4-yl)-2-(3,5-difluorophenyl)ethylcarbamate (**172A**):

- 5 Synthesis of (S)-tert-butyl 1-(5-(1H-pyrrolo[2,3-b]pyridin-5-yl)pyrimidin-4-yl)-2-(3,5-difluorophenyl)ethylcarbamate (**172B**):

The title compound as prepared according to the method presented in the synthesis of **136B** in Example 136 utilizing **172A** and 1H-pyrrolo[2,3-b]pyridin-5-ylboronic acid to provide the title compound. MS (*m/z*) 451.8 [M+H]⁺.

10

Synthesis of (S)-1-(5-(1H-pyrrolo[2,3-b]pyridin-5-yl)pyrimidin-4-yl)-2-(3,5-difluorophenyl)ethanamine (**172C**):

The title compound as prepared according to the method presented in the synthesis of **136C** in Example 136 utilizing (S)-tert-butyl 1-(5-(1H-pyrrolo[2,3-b]pyridin-5-yl)pyrimidin-4-yl)-2-(3,5-difluorophenyl)ethylcarbamate to provide the title compound.

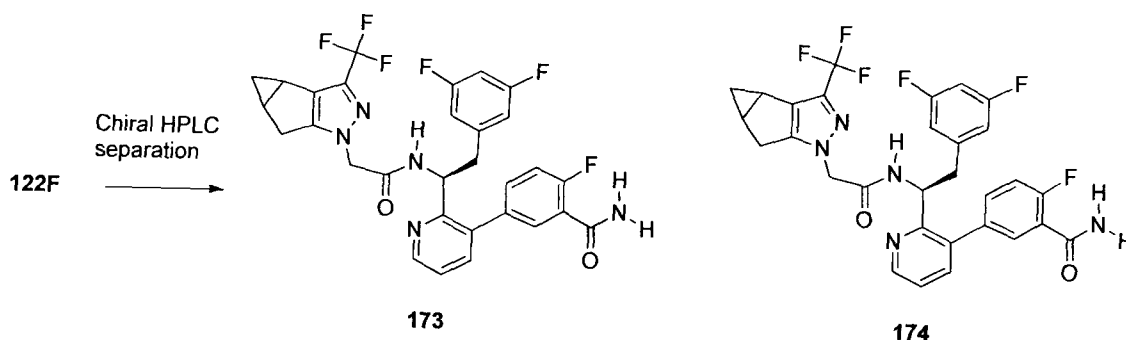
15

Synthesis of N-((S)-1-(5-(1H-pyrrolo[2,3-b]pyridin-5-yl)pyrimidin-4-yl)-2-(3,5-difluorophenyl)ethyl)-2-(3-(difluoromethyl)-5,5-difluoro-3b,4,4a,5-tetrahydro-1H-cyclopropa[3,4]cyclopenta[1,2-c]pyrazol-1-yl)acetamide (**172D**):

- 20 The title compound as prepared (4 mg) according to the method presented in the synthesis of Example 54 utilizing **60G** and **172C**. ¹H NMR (400 MHz, cd₃cn) δ 12.37 (s, 1H), 9.26 (s, 1H), 8.59 (s, 1H), 8.20 (d, 1H), 8.08 (d, 1H), 7.70 (s, 1H), 7.42 (s, 3H), 6.89 (d, 1H), 6.74 (dd, 2H),

6.62 (d, 1H), 6.37 (d, 2H), 5.30 (d, 1H), 4.74 (p, 2H), 3.02 (t, 2H), 2.48 (s, 2H), 1.95 (dt), 1.39 (dd, 1H), 1.01 (s, 1H). MS (m/z) 598.1 $[M+H]^+$.

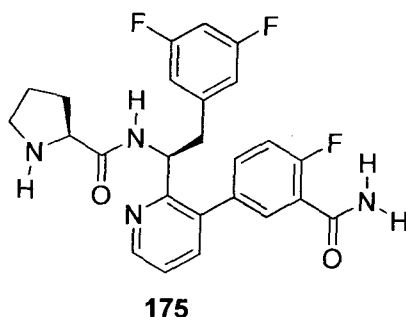
Examples 173 and 174



Synthesis of 5-(2-((S)-2-(3,5-difluorophenyl)-1-(2-((3bR,4aR)-3-(trifluoromethyl)-3b,4,4a,5-tetrahydro-1H-cyclopropa[3,4]cyclopenta[1,2-c]pyrazol-1-yl)acetamido)ethyl)pyridin-3-yl)-2-fluorobenzamide and 5-(2-((S)-2-(3,5-difluorophenyl)-1-(2-((3bS,4aS)-3-(trifluoromethyl)-3b,4,4a,5-tetrahydro-1H-cyclopropa[3,4]cyclopenta[1,2-c]pyrazol-1-yl)acetamido)ethyl)pyridin-3-yl)-2-fluorobenzamide (**173** and **174**):

The title compounds were separated from the diastereomeric mixture **122F** by semi-preparative chiral HPLC fitted with a Chiralpak IC column running a 70:30 mixture of Hep:IPA to obtain the desired compounds as pure diastereomers: **173** (14 mg): HPLC $rt=$ 11.5 min; MS (m/z) 600.4 $[M+H]^+$. **174** (12 mg): HPLC $rt=$ 13.5 min; MS (m/z) 600.4 $[M+H]^+$. Absolute stereochemistry is unknown.

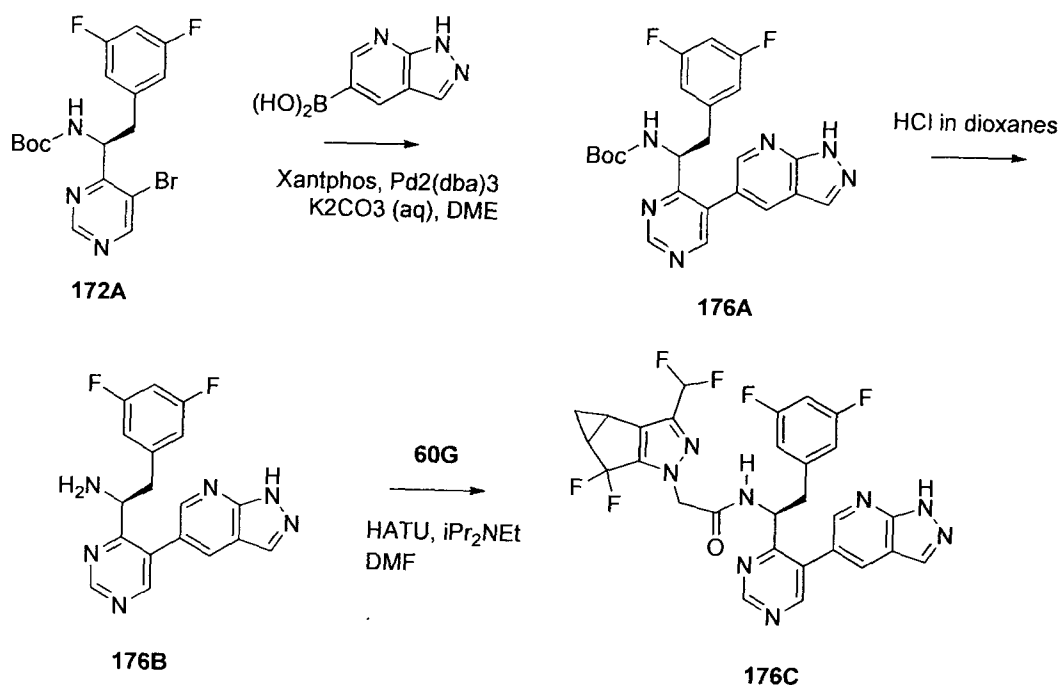
Example 175



Synthesis of (S)-N-((S)-1-(3-(3-carbamoyl-4-fluorophenyl)pyridin-2-yl)-2-(3,5-difluorophenyl)ethyl)pyrrolidine-2-carboxamide (**175**):

The title compound was prepared (4 mg) according to the method presented in the synthesis of Example 125 utilizing **171**. MS (m/z) 469.4 $[M+H]^+$.

Example 176



Synthesis of (S)-tert-butyl 1-(5-(1H-pyrazolo[3,4-b]pyridin-5-yl)pyrimidin-4-yl)-2-(3,5-difluorophenyl)ethylcarbamate (**176A**):

The title compound as prepared according to the method presented in the synthesis of **136B** in Example 136 utilizing **172A** and 1H-pyrazolo[3,4-b]pyridin-5-ylboronic acid to provide the title compound. MS (*m/z*) 452.8 [*M*+*H*]⁺.

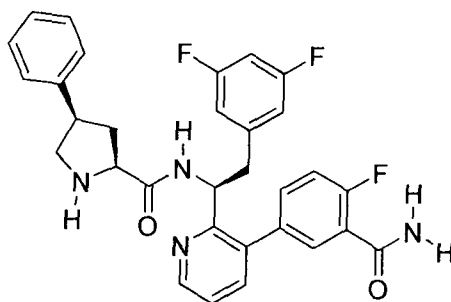
Synthesis of (S)-1-(5-(1H-pyrazolo[3,4-b]pyridin-5-yl)pyrimidin-4-yl)-2-(3,5-difluorophenyl)ethanamine (**176B**):

The title compound as prepared according to the method presented in the synthesis of **136C** in Example 136 utilizing (S)-tert-butyl 1-(5-(1H-pyrazolo[3,4-b]pyridin-5-yl)pyrimidin-4-yl)-2-(3,5-difluorophenyl)ethylcarbamate to provide the title compound.

Synthesis of N-((S)-1-(5-(1H-pyrazolo[3,4-b]pyridin-5-yl)pyrimidin-4-yl)-2-(3,5-difluorophenyl)ethyl)-2-(3-(difluoromethyl)-5,5-difluoro-3b,4,4a,5-tetrahydro-1H-cyclopropa[3,4]cyclopenta[1,2-c]pyrazol-1-yl)acetamide (**176C**):

The title compound as prepared (2 mg) according to the method presented in the synthesis of Example 54 utilizing **60G** and **176B**. ¹H NMR (400 MHz, *cd*₃cn) δ 9.23 (s, 1H), 8.58 (d, 1H), 8.29 (s, 1H), 8.10 (d, 1H), 7.88 (d, 1H), 7.37 (d, 1H), 6.89 (d, 1H), 6.73 (dd, 2H), 6.62 (d, 1H), 6.33 (d, 2H), 5.33 (q, 1H), 4.87 – 4.65 (m, 3H), 2.99 (dd, 3H), 2.48 (s, 2H), 1.95 (dt), 1.39 (dd, 1H), 1.01 (s, 1H). MS (*m/z*) 599.0 [*M*+*H*]⁺.

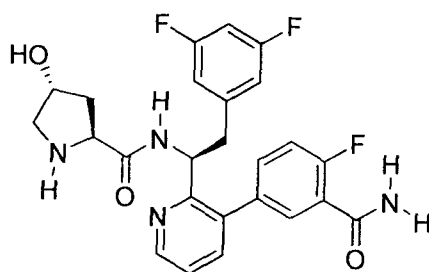
Example 177

**177**

Synthesis of (2S,4R)-N-((S)-1-(3-(3-carbamoyl-4-fluorophenyl)pyridin-2-yl)-2-(3,5-difluorophenyl)ethyl)-4-phenylpyrrolidine-2-carboxamide (**177**):

- 5 The title compound was prepared (11 mg) according to the method presented in the synthesis of Example 125 utilizing **148**. MS (m/z) 545.2 $[M+H]^+$.

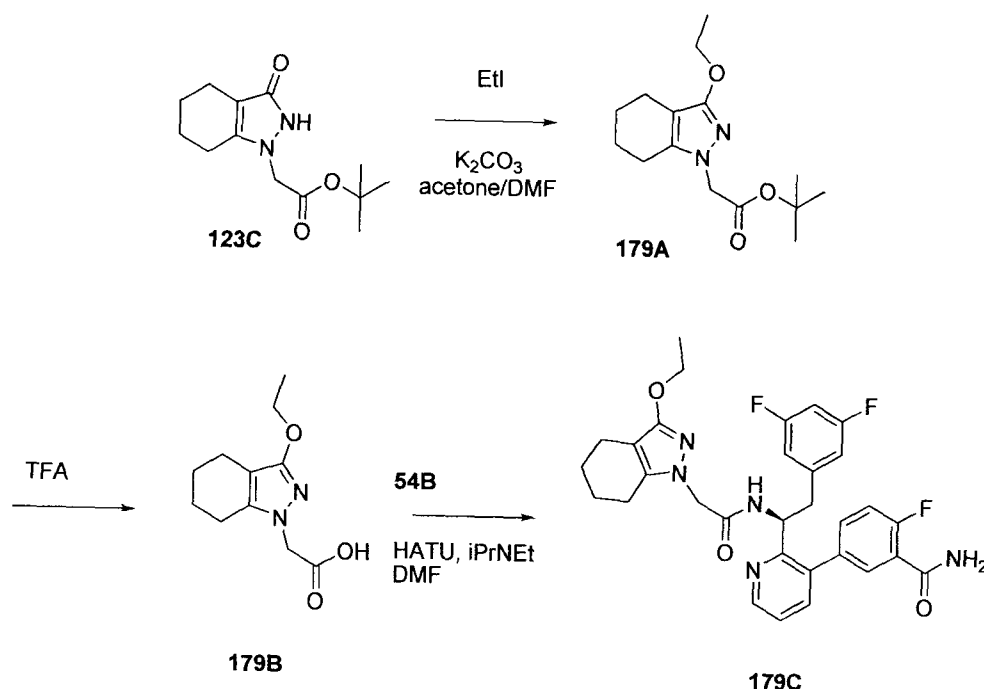
Example 178

**178**

- 10 Synthesis of (2S,4R)-N-((S)-1-(3-(3-carbamoyl-4-fluorophenyl)pyridin-2-yl)-2-(3,5-difluorophenyl)ethyl)-4-hydroxypyrrolidine-2-carboxamide (**178**):

The title compound was prepared (10 mg) according to the method presented in the synthesis of Example 125 utilizing **132**. MS (m/z) 485.4 $[M+H]^+$.

- 15 Example 179



Synthesis of tert-butyl 2-(3-ethoxy-4,5,6,7-tetrahydro-1H-indazol-1-yl)acetate (**179A**):

Under the conditions described for the synthesis of **170A** in Example 170, the title compound was synthesized as the major regioisomer exhibiting a shorter retention time on HPLC: MS

(*m/z*) 281.1 [$\text{M}+\text{H}$]⁺.

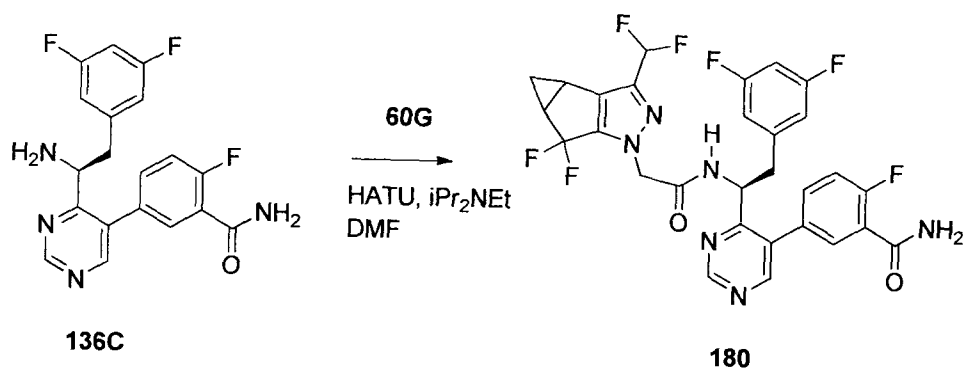
Synthesis of 2-(3-ethoxy-4,5,6,7-tetrahydro-1H-indazol-1-yl)acetic acid (**179B**):

The title compound was prepared according to the method presented in the synthesis of **170B** in Example 170: MS (*m/z*) 225.2 [$\text{M}+\text{H}$]⁺.

Synthesis of (S)-5-(2-(2-(3,5-difluorophenyl)-1-(2-(3-ethoxy-4,5,6,7-tetrahydro-1H-indazol-1-yl)acetamido)ethyl)pyridin-3-yl)-2-fluorobenzamide (**179C**):

The title compound was prepared (70 mg) according to the method presented in the synthesis of Example 54 utilizing **54B** and 2-(3-ethoxy-4,5,6,7-tetrahydro-1H-indazol-1-yl)acetic acid. ¹H NMR (400 MHz, cd_3od) δ 8.66 (dd, 1H), 7.68 (dd, 1H), 7.56 – 7.43 (m, 2H), 7.34 (s, 1H), 7.25 (dd, 1H), 6.67 (t, 1H), 6.32 (d, 2H), 5.38 (t, 1H), 4.84 (s, 10H), 4.52 (s, 2H), 4.14 (q, 2H), 3.29 (dt, 9H), 2.99 (d, 2H), 2.34 (dt, 4H), 1.78 – 1.64 (m, 4H), 1.33 (t, 3H). MS (*m/z*) 578.7 [$\text{M}+\text{H}$]⁺.

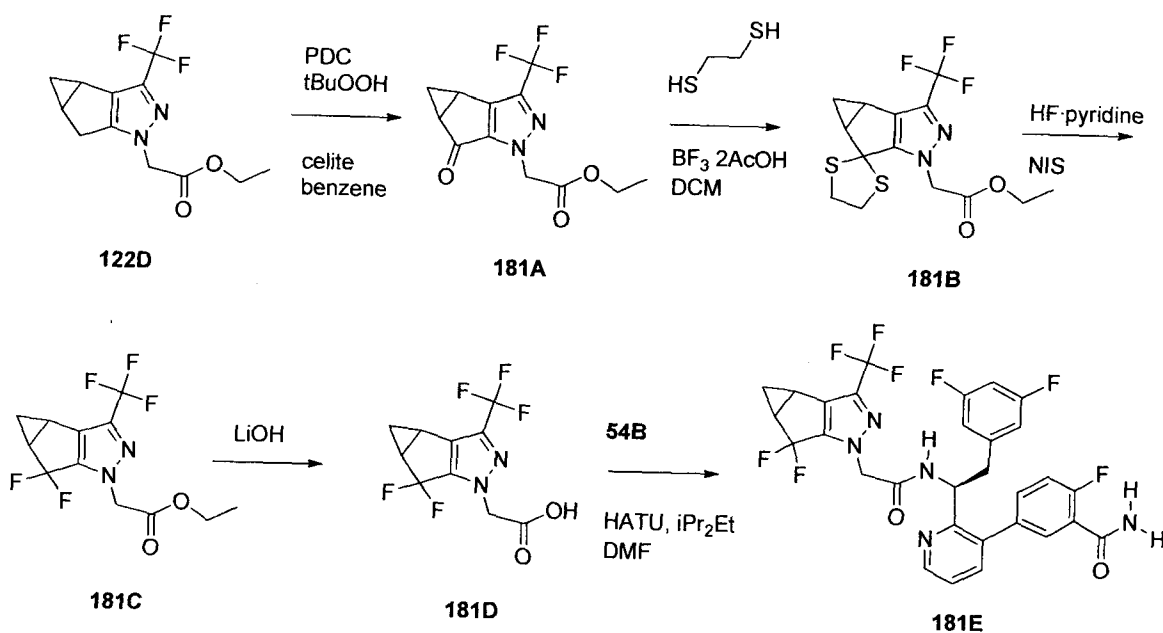
Example 180



Synthesis of 5-(4-((1S)-1-(2-(3-(difluoromethyl)-5,5-difluoro-3b,4,4a,5-tetrahydro-1H-cyclopropa[3,4]cyclopenta[1,2-c]pyrazol-1-yl)acetamido)-2-(3,5-difluorophenyl)ethyl)pyrimidin-5-yl)-2-fluorobenzamide (**180**):

The title compound as prepared (51 mg) according to the method presented in the synthesis of Example 54 utilizing **60G** and **136C**. ^1H NMR (400 MHz, dmso) δ 9.25 (s, 1H), 9.11 (s, 1H), 8.62 (s, 1H), 7.66 (s, 2H), 7.52 (s, 1H), 7.36 (d, 1H), 6.92 (s, 2H), 6.59 (s, 2H), 5.11 (s, 1H), 4.70 (d, 3H), 3.37 (bs), 3.00 (d, 3H), 2.51 – 2.42 (m), 1.33 (s, 1H), 0.87 (s, 1H). MS (m/z) 619.3 $[\text{M}+\text{H}]^+$.

Example 181



Synthesis of ethyl 2-(5-oxo-3-(trifluoromethyl)-3b,4,4a,5-tetrahydro-1H-cyclopropa[3,4]cyclopenta[1,2-c]pyrazol-1-yl)acetate (**181A**):

Ethyl 2-(3-(trifluoromethyl)-3b,4,4a,5-tetrahydro-1H-cyclopropa[3,4]cyclopenta[1,2-c]pyrazol-1-yl)acetate (1.92 g, 7 mmol) and celite 545 (1 g / mmol) was combined in benzene (50 mL) and cooled to 5 °C (just above freezing). PDC (10.5 g, 28 mmol) was added followed by tert-butylhydroperoxide (5-6 M solution in decane, 5.1 mL, 28 mmol). The solution was let warm to ambient temperature, then stirred for 3 days. The reaction is filtered over celite, eluted with EtOAc, and the solvents removed in vacuo. Crude residue is resubjected to the same reaction conditions and let stir for 1 day. The reaction is again filtered over celite, eluted with EtOAc, and the solvents removed in vacuo to provide the title compound (1.1 g) as a mixture with **122D** (ratio determined by ¹⁹F NMR): MS (*m/z*) 289.0 [M+H]⁺.

Synthesis of ethyl 2-(3-(trifluoromethyl)-4,4a-dihydrospiro[cyclopropa[3,4]cyclopenta[1,2-c]pyrazole-5,2'-[1,3]dithiolane]-1(3bH)-yl)acetate (**181B**):

Ethyl 2-(5-oxo-3-(trifluoromethyl)-3b,4,4a,5-tetrahydro-1H-cyclopropa[3,4]cyclopenta[1,2-c]pyrazol-1-yl)acetate (1.1 g, 3.8 mmol) and ethanediol (0.54 mL, 6.4 mmol) were combined in DCM (12 mL) to which BF₃ acetic acid complex (0.88 mL, 6.4 mmol) was added. The reaction was stirred at ambient temperature for 3 h. LCMS shows complete conversion of keto- starting material to product. The reaction was cooled to 0 °C and quenched with saturated aqueous NaHCO₃. The organics were separated and dried with saturated aqueous NaCl. Solvents were removed in vacuo and the residue purified by column chromatography on silica to provide 900 mg of the title compound product as a mixture with compound **122D**. MS (*m/z*) 365.1 [M+H]⁺.

Synthesis of ethyl 2-(5,5-difluoro-3-(trifluoromethyl)-3b,4,4a,5-tetrahydro-1H-cyclopropa[3,4]cyclopenta[1,2-c]pyrazol-1-yl)acetate (**181C**):

In a teflon bottle, NIS (1.34 g, 5.93 mmol) was suspended in DCM (1.5 mL) and cooled to -78 °C. HF pyridine (4 mL) added. Ethyl 2-(3-(trifluoromethyl)-4,4a-dihydrospiro[cyclopropa[3,4]cyclopenta[1,2-c]pyrazole-5,2'-[1,3]dithiolane]-1(3bH)-yl)acetate was dissolved in DCM (2.5 mL) and added dropwise. The reaction was stirred 30 min at -78 °C then let slowly warm to -30 °C. The reaction was held at -30 °C for 3 h. To a 1 L beaker charged with saturated aqueous NaHCO₃ (100 mL), ice was added to increase volume to 250 ml and stirred vigorously. The reaction was poured into the basic quench solution. The solution was extracted with EtOAc (3x), organics separated and dried with saturated aqueous NaCl. Solvents were removed in vacuo and the residue purified by column chromatography on silica to provide the title compound (320 mg): MS (*m/z*) 311.0 [M+H]⁺.

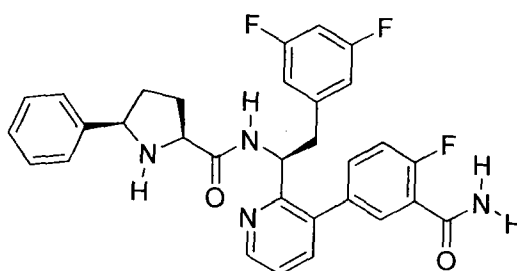
Synthesis of 2-(5,5-difluoro-3-(trifluoromethyl)-3b,4,4a,5-tetrahydro-1H-cyclopropa[3,4]cyclopenta[1,2-c]pyrazol-1-yl)acetic acid (**181D**):

- The title compound was prepared according to the method presented in the synthesis of **122F** in Example 122 utilizing **181C**. MS (m/z) 283.0 $[M+H]^+$.

Synthesis of 5-(2-((1S)-1-(2-(5,5-difluoro-3-(trifluoromethyl)-3b,4,4a,5-tetrahydro-1H-cyclopropa[3,4]cyclopenta[1,2-c]pyrazol-1-yl)acetamido)-2-(3,5-difluorophenyl)ethyl)pyridin-3-yl)-2-fluorobenzamide (**181E**):

- The title compound (10 mg) was prepared according to the method presented in the synthesis of Example 54 utilizing **54B** and **181D**. ^1H NMR (400 MHz, dmso) δ 8.97 (s, 1H), 8.67 (d, 1H), 7.75 – 7.57 (m, 3H), 7.41 (dd, 2H), 7.35 – 7.24 (m, 1H), 6.88 (s, 1H), 6.53 (s, 2H), 5.14 (s, 1H), 4.77 (dt, 4H), 3.88 (bs), 2.98 (d, 2H), 2.51 – 2.42 (m), 1.36 (s, 1H), 0.96 (s, 1H). MS (m/z) 636.1 $[M+H]^+$.

Example 182

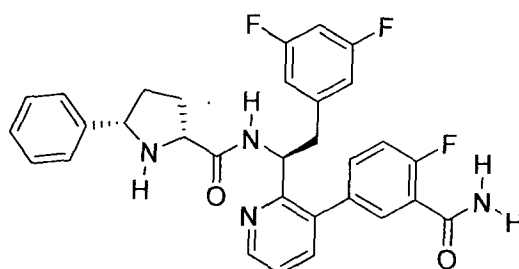


182

Synthesis of (2S,5R)-N-((S)-1-(3-(3-carbamoyl-4-fluorophenyl)pyridin-2-yl)-2-(3,5-difluorophenyl)ethyl)-5-phenylpyrrolidine-2-carboxamide (**182**):

- The title compound was prepared (3 mg) according to the method presented in the synthesis of Example 125 utilizing **139**. MS (m/z) 545.3 $[M+H]^+$.

Example 183



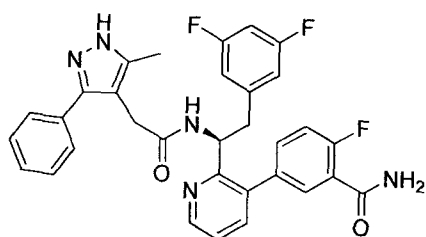
183

Synthesis of (2R,5S)-N-((S)-1-(3-(3-carbamoyl-4-fluorophenyl)pyridin-2-yl)-2-(3,5-difluorophenyl)ethyl)-5-phenylpyrrolidine-2-carboxamide (**183**):

The title compound was prepared (3 mg) according to the method presented in the synthesis of Example 125 utilizing **158**. MS (m/z) 545.3 $[M+H]^+$.

5

Example 184



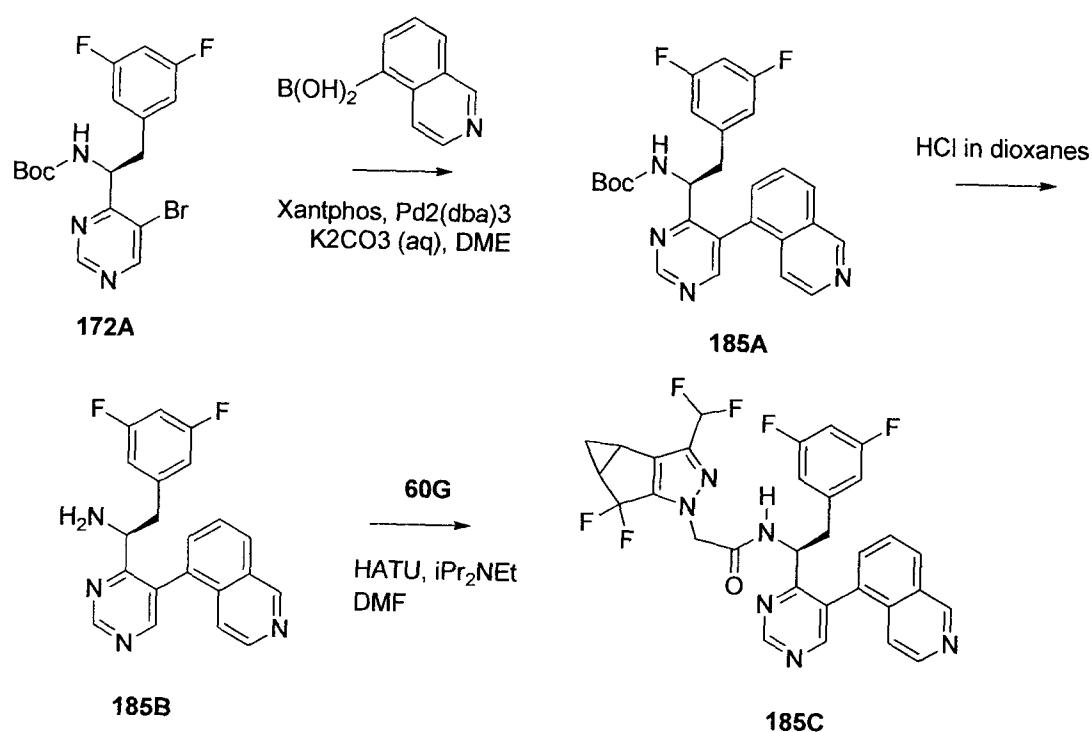
184

Synthesis of (S)-5-(2-(2-(3,5-difluorophenyl)-1-(2-(5-methyl-3-phenyl-1H-pyrazol-4-yl)acetamido)ethyl)pyridin-3-yl)-2-fluorobenzamide (**184**):

10 The title compound was prepared (9 mg) according to the method presented in the synthesis of Example 54 utilizing **54B** and 2-(5-methyl-3-phenyl-1H-pyrazol-4-yl)acetic acid. ^1H NMR (400 MHz, dmsO) δ 8.66 (d, 1H), 8.51 (d, 1H), 7.62 (dd, 2H), 7.54 – 7.36 (m, 4H), 7.36 – 7.02 (m, 3H), 6.92 (t, 1H), 6.53 (d, 2H), 5.17 (d, 1H), 3.26 (s, 2H), 2.95 (d, 2H), 2.52 – 2.42 (m, 13H), 1.99 (s, 2H), 1.87 (s, 1H). MS (m/z) 570.8 $[M+H]^+$.

15

Example 185



Synthesis of (S)-tert-butyl 2-(3,5-difluorophenyl)-1-(5-(isoquinolin-5-yl)pyrimidin-4-yl)ethylcarbamate (**185A**):

- The title compound as prepared according to the method presented in the synthesis of **136B** in Example 136 utilizing **172A** and isoquinolin-6-ylboronic acid to provide the title compound. MS (m/z) 463.3 $[M+H]^+$.

Synthesis of (S)-2-(3,5-difluorophenyl)-1-(5-(isoquinolin-5-yl)pyrimidin-4-yl)ethanamine (**185B**):

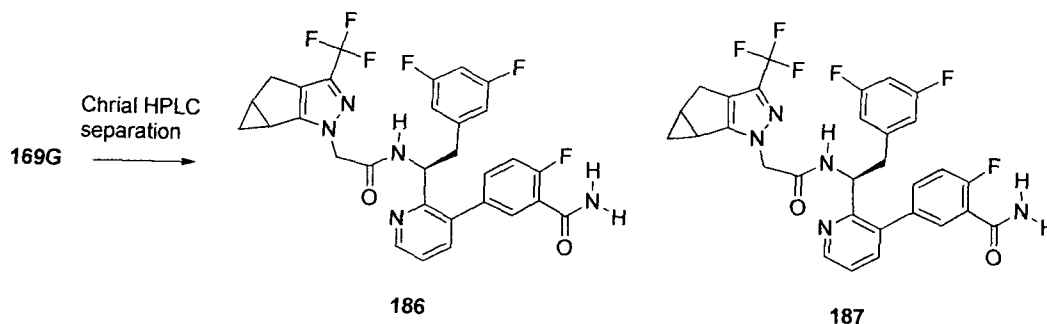
- The title compound as prepared according to the method presented in the synthesis of **136C** in Example 136 utilizing (S)-tert-butyl 2-(3,5-difluorophenyl)-1-(5-(isoquinolin-5-yl)pyrimidin-4-yl)ethylcarbamate to provide the title compound.

Synthesis of 2-(3-(difluoromethyl)-5,5-difluoro-3b,4,4a,5-tetrahydro-1H-cyclopropa[3,4]cyclopenta[1,2-c]pyrazol-1-yl)-N-((S)-2-(3,5-difluorophenyl)-1-(5-(isoquinolin-5-yl)pyrimidin-4-yl)ethyl)acetamide (**185C**):

- The title compound as prepared (4 mg) according to the method presented in the synthesis of Example 54 utilizing **60G** and **185B**. The title compound exists as a mixture of rotational isomers which was confirmed by a high temperature NMR experiment. ^1H NMR (400 MHz, dmso) δ 9.62 (s, 1H), 9.56 (s, 1H), 9.44 – 9.38 (m, 1H), 9.05 (d, 1H), 8.88 (t, 1H), 8.75 – 8.67 (m, 2H), 8.46 – 8.29 (m, 3H), 8.01 – 7.60 (m, 3H), 7.58 (d, 1H), 7.36 (s, 1H), 7.10 – 6.92 (m,

3H), 6.92 – 6.68 (m, 2H), 6.44 (s, 2H), 6.21 (d, 2H), 4.90 (d, 2H), 4.78 – 4.45 (m, 8H), 2.97 (t, 3H), 2.91 – 2.82 (m, 1H), 2.50 – 2.41 (m), 1.34 (d, 2H), 0.88 (s, 1H), 0.81 (s, 1H). MS (m/z) 609.4 $[M+H]^+$.

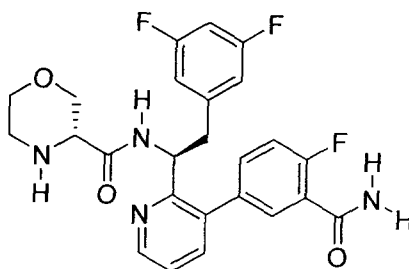
5 Examples 186 and 187



Synthesis of 5-(2-((S)-2-(3,5-difluorophenyl)-1-(2-(((4aS,5aS)-3-(trifluoromethyl)-4,4a,5,5a-tetrahydro-1H-cyclopropa[4,5]cyclopenta[1,2-c]pyrazol-1-yl)acetamido)ethyl)pyridin-3-yl)-2-fluorobenzamide and 5-(2-((S)-2-(3,5-difluorophenyl)-1-(2-(((4aR,5aR)-3-(trifluoromethyl)-4,4a,5,5a-tetrahydro-1H-cyclopropa[4,5]cyclopenta[1,2-c]pyrazol-1-yl)acetamido)ethyl)pyridin-3-yl)-2-fluorobenzamide (**186** and **187**):

The title compounds were separated from the diastereomeric mixture **169G** by semi-preparative chiral HPLC fitted with a Chiralpak IC column running a 70:30 mixture of Hep:IPA to obtain the desired compounds as pure diastereomers: **186** (4 mg): HPLC rt = 12.4 min; MS (m/z) 600.4 $[M+H]^+$. **187** (3 mg): HPLC rt = 14.0 min; MS (m/z) 600.4 $[M+H]^+$. Absolute stereochemistry is unknown.

Example 188

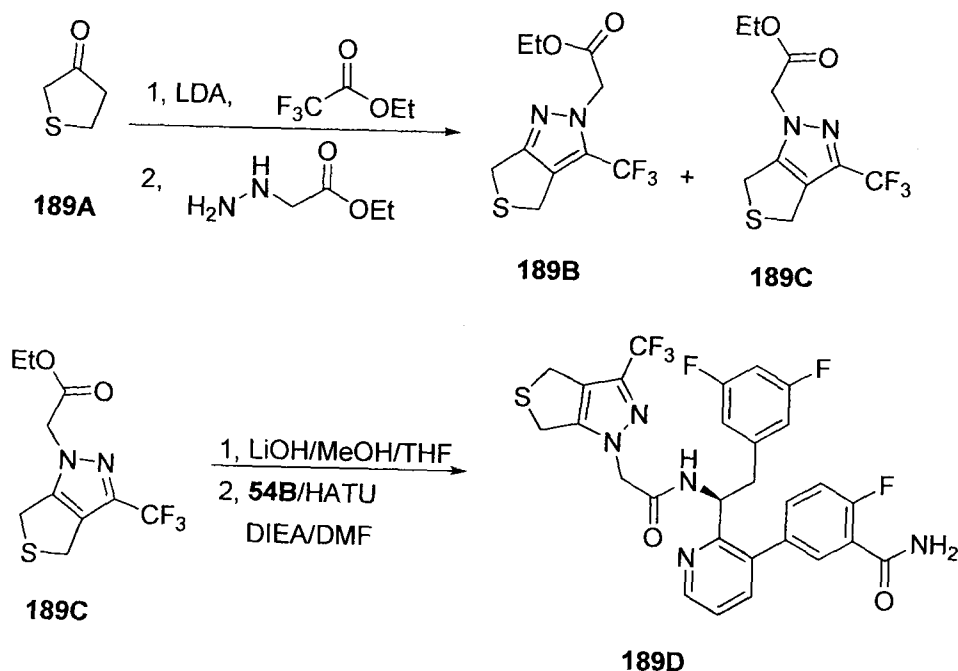


188

Synthesis of (R)-N-((S)-1-(3-(3-carbamoyl-4-fluorophenyl)pyridin-2-yl)-2-(3,5-difluorophenyl)ethyl)morpholine-3-carboxamide (**188**):

The title compound was prepared (6 mg) according to the method presented in the synthesis of Example 125 utilizing **133**.

Example 189



- 5 Synthesis of ethyl 2-(3-(trifluoromethyl)-4,6-dihydro-2H-thieno[3,4-c]pyrazol-2-yl)acetate (**189B**) and 300mg of ethyl 2-(3-(trifluoromethyl)-4,6-dihydro-1H-thieno[3,4-c]pyrazol-1-yl)acetate (**189C**)

Compound **189B** and **189C** were prepared according to the method presented for the synthesis of Example 122 substituting dihydrothiophen-3(2H)-one for **122B** to provide 80 mg of **189B** and

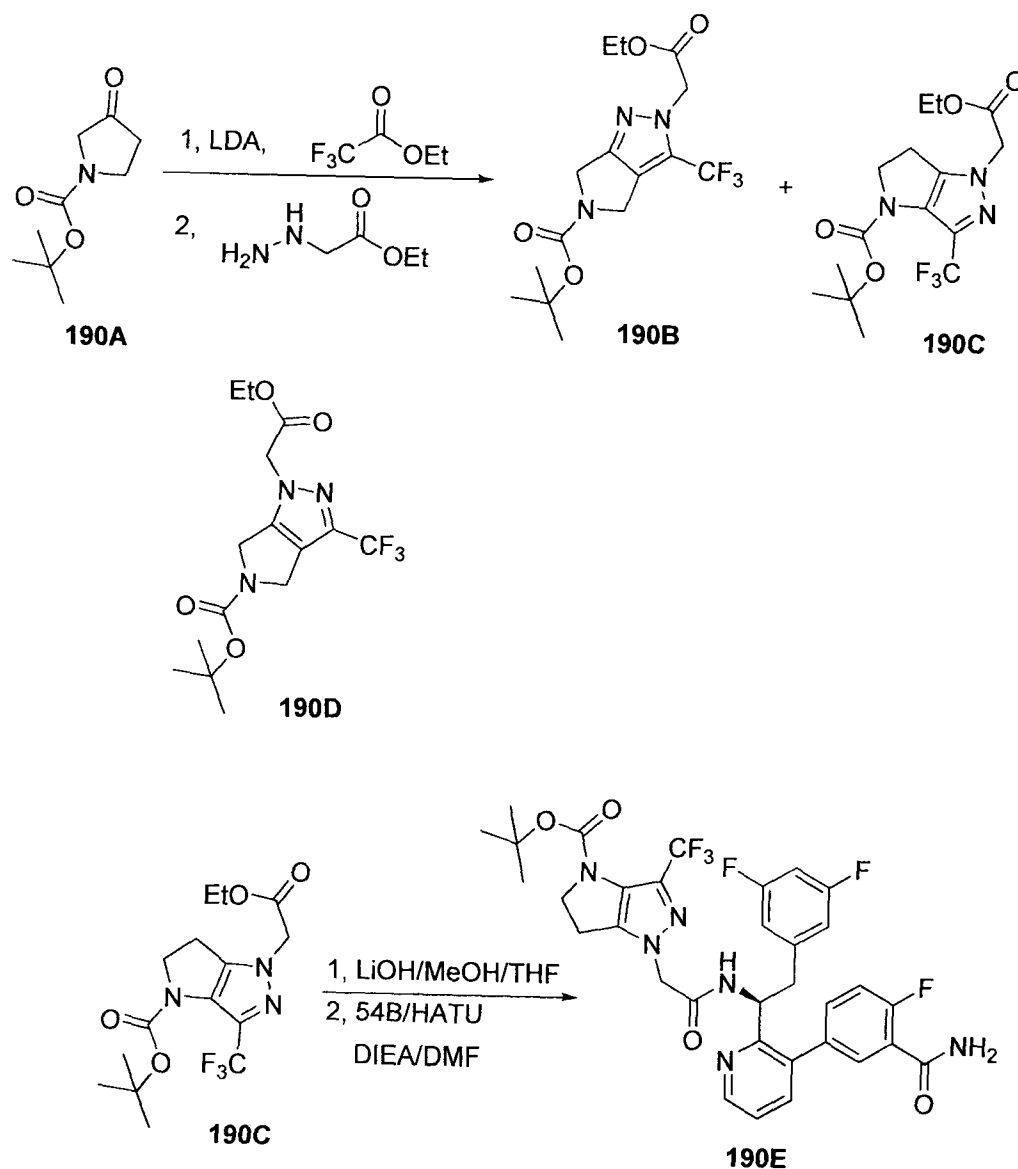
10 300 mg of **189C**. **189B**: MS (m/z) 281 [$\text{M}+\text{H}$] $^+$ and **189C**: MS (m/z) 281 [$\text{M}+\text{H}$] $^+$.

Synthesis of (S)-5-(2-(2-(3,5-difluorophenyl)-1-(2-(3-(trifluoromethyl)-4,6-dihydro-1H-thieno[3,4-c]pyrazol-1-yl)acetamido)ethyl)pyridin-3-yl)-2-fluorobenzamide (**189D**):

Compound **189D** was prepared according to the method presented for the synthesis of Example

15 122 substituting **189C** for **122D** to provide 18 mg of title compound: ^1H NMR (400 MHz, cd_3od) δ 8.76 – 8.68 (m, 1H), 7.72 – 7.63 (m, 1H), 7.52 – 7.42 (m, 1H), 7.42 – 7.25 (m, 2H), 7.25 – 7.17 (m, 1H), 6.67 (t, 1H), 6.32 (d, 2H), 5.35 (t, 1H), 4.91 (s, 2H), 3.94 (d, 4H), 3.05 (d, 2H). MS (m/z) 606 [$\text{M}+\text{H}$] $^+$.

20 Example 190



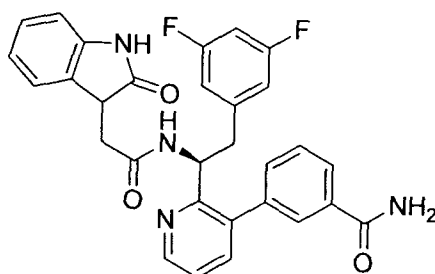
Synthesis of tert-butyl 2-(2-ethoxy-2-oxoethyl)-3-(trifluoromethyl)-4,6-dihydropyrrolo[3,4-c]pyrazole-5(2H)-carboxylate (**190B**), tert-butyl 1-(2-ethoxy-2-oxoethyl)-3-(trifluoromethyl)-5,6-dihydropyrrolo[3,2-c]pyrazole-4(1H)-carboxylate (**190C**) and tert-butyl 1-(2-ethoxy-2-oxoethyl)-3-(trifluoromethyl)-4,6-dihydropyrrolo[3,4-c]pyrazole-5(1H)-carboxylate (**190D**):

Compound **190B**, **190C** and **190D** were prepared according to the method presented for the synthesis of Example 122 substituting tert-butyl 3-oxopyrrolidine-1-carboxylate for **122B** to provide 60 mg of **190B**, 35 mg of **190C** and 60 mg of **190D**. **190B**: MS (m/z) 364 [$M+H$]⁺, **190C**: MS (m/z) 364 [$M+H$]⁺ and **190D**: MS (m/z) 364 [$M+H$]⁺.

Synthesis of (S)-tert-butyl 1-(2-((1-(3-(3-carbamoyl-4-fluorophenyl)pyridin-2-yl)-2-(3,5-difluorophenyl)ethyl)amino)-2-oxoethyl)-3-(trifluoromethyl)-5,6-dihydropyrrolo[3,2-c]pyrazole-4(1H)-carboxylate (**190E**):

Compound 190E was prepared according to the method presented for the synthesis of Example 122 substituting **190C** for **122D** to provide 46 mg of title compound: ^1H NMR (400 MHz, cd_3od) δ 8.70 (d, 1H), 7.61 (d, 1H), 7.42 (d, 2H), 7.31 (s, 1H), 7.27 – 7.16 (m, 1H), 6.66 (t, 1H), 6.32 (d, 2H), 5.34 (t, 1H), 4.96 (s, 2H), 4.46 (dd, 4H), 3.06 (dd, 3H), 1.50 (s, 9H). MS (m/z) 689 $[\text{M}+\text{H}]^+$.

Example 191

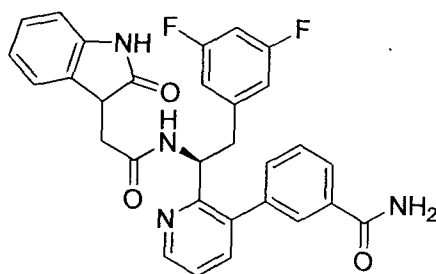


191

Synthesis of 3-(2-((1S)-2-(3,5-difluorophenyl)-1-(2-(2-oxoindolin-3-yl)acetamido)ethyl)pyridin-3-yl)benzamide (**191**):

Compound 191 was prepared according to the method presented for the synthesis of Example 50 utilizing **50C** and 2-(2-oxoindolin-3-yl)acetic acid to provide 44 mg of title compound: ^1H NMR (400 MHz, dmsO) δ 9.83 (d, 1H), 9.03 – 8.72 (m, 1H), 8.64 (d, 1H), 8.01 – 7.70 (m, 2H), 7.67 – 7.45 (m, 2H), 7.44 – 7.25 (m, 2H), 7.02 (dt, 1H), 6.86 (t, 1H), 6.71 (ddd, 2H), 6.47 (d, 2H), 5.19 – 4.96 (m, 1H), 3.82 (dt, 1H), 2.93 (dd, 2H), 2.40 – 2.16 (m, 2H).; MS (m/z) 527 $[\text{M}+\text{H}]^+$.

Example 192

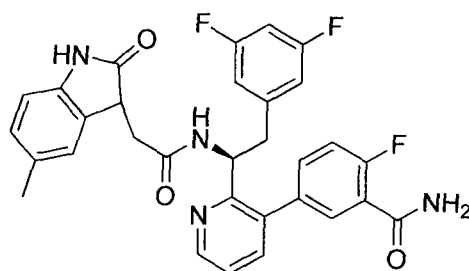


192

Synthesis of 3-(2-((1S)-2-(3,5-difluorophenyl)-1-(2-(2-oxoindolin-3-yl)acetamido)ethyl)pyridin-3-yl)benzamide (**192**):

Compound 192 was purified from compound **191** by RP HPLC using a C18 column with a gradient of H₂O, 0.1% TFA-acetonitrile. The fast eluent was collected and concentrated to provide 18 mg of title compound: ¹H NMR (400 MHz, dmso) δ 9.89 (s, 1H), 8.82 (d, 1H), 8.69 – 8.61 (m, 1H), 8.02 – 7.81 (m, 2H), 7.70 – 7.56 (m, 2H), 7.48 – 7.27 (m, 4H), 7.06 (t, 2H), 6.92 (t, 1H), 6.85 – 6.70 (m, 2H), 6.51 (d, 2H), 5.14 (d, 1H), 3.88 (t, 2H), 2.99 (d, 2H), 2.44 – 2.20 (m, 2H). MS (*m/z*) 527 [M+H]⁺.

Example 193

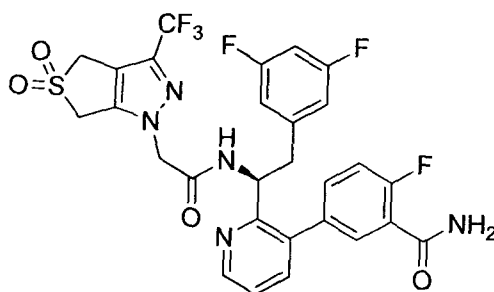


193

10 Synthesis of 5-(2-((1S)-2-(3,5-difluorophenyl)-1-(2-(5-methyl-2-oxoindolin-3-yl)acetamido)ethyl)pyridin-3-yl)-2-fluorobenzamide (**193**):

Compound 193 was prepared according to the method presented for the synthesis of Example 54 utilizing **54B** and 2-(5-methyl-2-oxoindolin-3-yl)acetic acid to provide 18 mg of title compound: ¹H NMR (400 MHz, cd₃od) δ 8.71 (s, 1H), 7.69 (dd, 1H), 7.49 (ddd, 1H), 7.45 – 7.07 (m, 3H), 7.07 – 6.57 (m, 5H), 6.27 (t, 2H), 5.34 (dd, 1H), 3.71 (t, 1H), 3.04 – 2.85 (m, 3H), 2.75 – 2.62 (m, 1H). MS (*m/z*) 559 [M+H]⁺.

Example 194

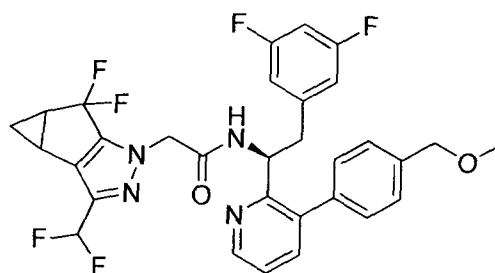


194

20 Synthesis of (S)-5-(2-(2-(3,5-difluorophenyl)-1-(2-(5,5-dioxido-3-(trifluoromethyl)-4,6-dihydro-1H-thieno[3,4-c]pyrazol-1-yl)acetamido)ethyl)pyridin-3-yl)-2-fluorobenzamide (**194**):

Compound 194 was prepared according to the method presented for the synthesis of Example 197 utilizing **189** (60 mg, 0.1 mmol), 3-Chloroperbenzoic acid (87 mg, 77% max., 0.2 mmol) in DCM (3 mL) at 0 °C to provide 20 mg of title compound: ^1H NMR (400 MHz, cd_3od) δ 8.61 (dd, 1H), 7.93 – 7.80 (m, 1H), 7.61 (s, 1H), 7.58 – 7.44 (m, 2H), 7.44 – 7.30 (m, 2H), 7.19 (ddd, 3H), 6.56 (tt, 1H), 6.23 (dd, 2H), 5.38 (s, 1H), 5.25 (dd, 1H), 4.91 (d, 2H), 4.75 (s, 5H), 4.45 – 4.18 (m, 4H), 4.00 (dd, 1H), 3.21 (dt, 3H), 3.09 – 2.86 (m, 2H), 2.22 – 2.03 (m, 1H), 1.91 (s, 1H), 1.17 (dd, , 2H), 1.13 – 0.97 (m, 1H), 0.80 (dd, 1H). MS (m/z) 638 [$\text{M}+\text{H}$] $^+$

Example 195

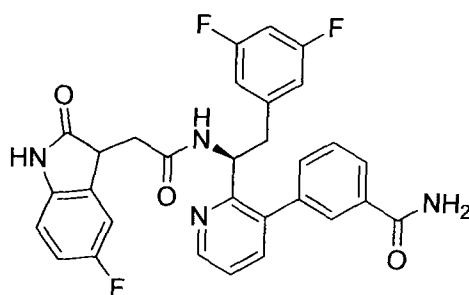


195

Synthesis of 2-(3-(difluoromethyl)-5,5-difluoro-3b,4,4a,5-tetrahydro-1H-cyclopropa[3,4]cyclopenta[1,2-c]pyrazol-1-yl)-N-((S)-2-(3,5-difluorophenyl)-1-(3-(4-(methoxymethyl)phenyl)pyridin-2-yl)ethyl)acetamide (**195**):

Compound 195 was prepared according to the method presented for the synthesis of Example 68 utilizing **68A** and (4-(methoxymethyl)phenyl)boronic acid to provide 13 mg of title compound: ^1H NMR (400 MHz, cd_3od) δ 8.65 (d, 1H), 7.63 (dd, 8.0 Hz, 2H), 7.45 (dd, 2H), 7.35 (dd, 3H), 7.14 – 7.01 (m, 2H), 6.68 (ddd, 3H), 6.24 (d, 2H), 5.44 (dd, 1H), 4.48 (d, 2H), 3.38 (s, 3H), 2.97 (dd, 2H), 2.56 – 2.34 (m, 2H), 1.37 (s, 1H), 1.04 (d, 1H). MS (m/z) 601 [$\text{M}+\text{H}$] $^+$.

Example 196



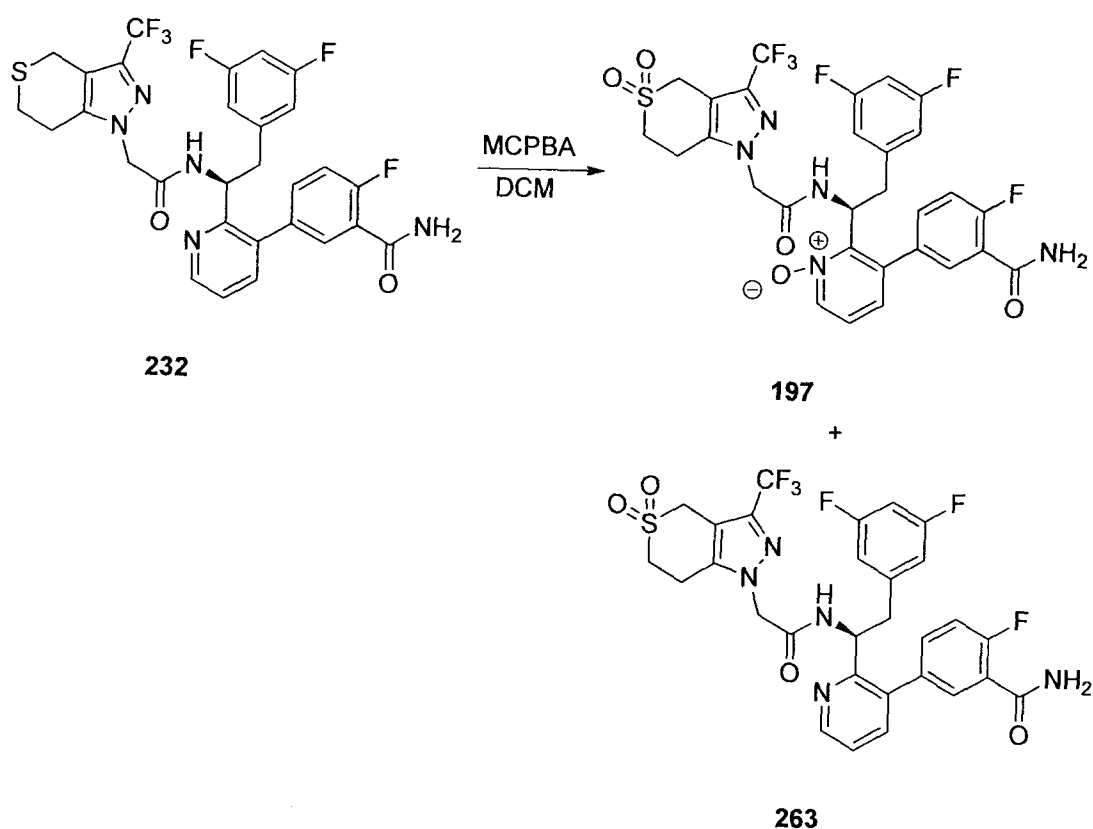
196

Synthesis of 3-(2-((1S)-2-(3,5-difluorophenyl)-1-(2-(5-fluoro-2-oxoindolin-3-yl)acetamido)ethyl)pyridin-3-yl)benzamide (**196**):

Compound **196** was prepared according to the method presented for the synthesis of Example 50 utilizing **50C** and 2-(5-fluoro-2-oxoindolin-3-yl)acetic acid to provide 27 mg of title compound:

¹H NMR (400 MHz, dmsO) δ 9.89 (d, 1H), 8.89 (dd, 1H), 8.66 (dd, 1H), 8.07 – 7.72 (m, 2H), 7.72 – 7.50 (m, 2H), 7.50 – 7.23 (m, 3H), 7.13 – 6.59 (m, 4H), 6.47 (d, 2H), 5.22 – 5.02 (m, 1H), 3.92 – 3.79 (m, 1H), 2.95 (dd, 2H), 2.34 (ddd, 1H). MS (*m/z*) 545 [M+H]⁺.

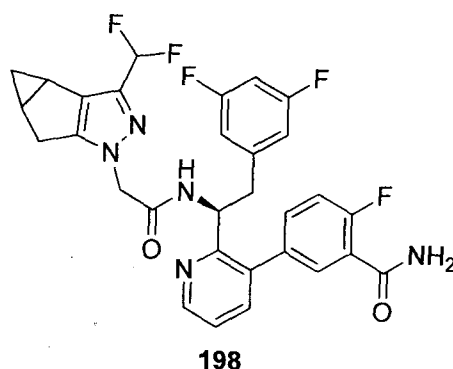
Example 197



Synthesis of (S)-3-(3-carbamoyl-4-fluorophenyl)-2-(2-(3,5-difluorophenyl)-1-(2-(5,5-dioxido-3-(trifluoromethyl)-6,7-dihydrothiopyrano[4,3-c]pyrazol-1(4H)-yl)acetamido)ethyl)pyridine-1-oxide (**197**) and (S)-5-(2-(2-(3,5-difluorophenyl)-1-(2-(5,5-dioxido-3-(trifluoromethyl)-6,7-dihydrothiopyrano[4,3-c]pyrazol-1(4H)-yl)acetamido)ethyl)pyridin-3-yl)-2-fluorobenzamide (**263**): **232** (120 mg, 0.194 mmol) and 3-Chloroperbenzoic acid (87 mg, 77% max., 0.2 mmol) in DCM (5 mL) at 0 °C, was stirred for 2 hours. Solvents were concentrated *in vacuo* and the residue was purified by RP HPLC using a C18 column with a gradient of H₂O, 0.1% TFA-acetonitrile, to provide 25 mg of **197** and 27 mg of **263**: ¹H NMR (400 MHz, cd3od) δ 8.94 (d,

1H), 8.33 (d, 1H), 7.92 – 7.79 (m, 1H), 7.51 – 7.30 (m, 3H), 7.19 – 7.09 (m, 1H), 6.65 (t, 1H), 6.34 (d, 2H), 5.46 – 5.29 (m, 1H), 4.85 (d, 2H), 4.19 (s, 2H), 3.18 – 2.94 (m, 4H), 0.02 – 3.24 (m, 6H), 3.57 – 3.44 (m, 1H), 3.31 (d, 2H); MS (*m/z*) 668 [M+H]⁺.

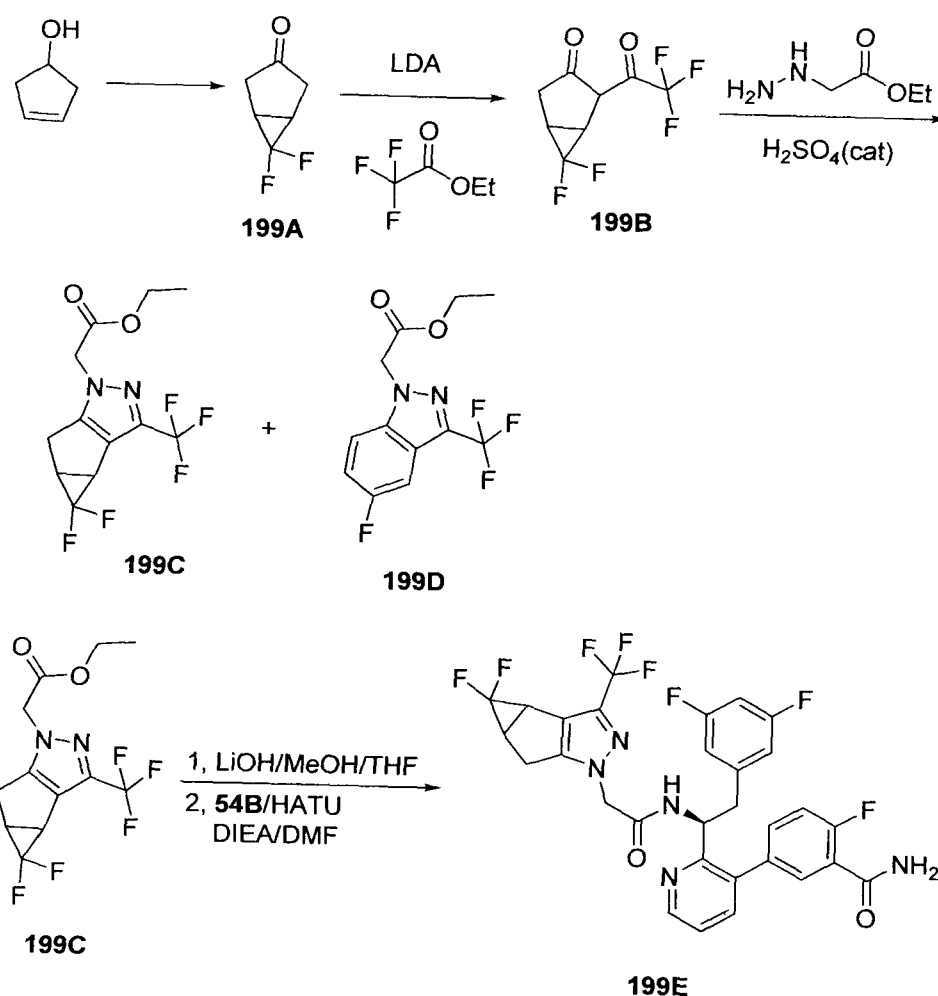
5 Example 198



Synthesis of 5-(2-((1S)-1-(2-(3-(difluoromethyl)-3b,4,4a,5-tetrahydro-1H-cyclopropa[3,4]cyclopenta[1,2-c]pyrazol-1-yl)acetamido)-2-(3,5-difluorophenyl)ethyl)pyridin-3-yl)-2-fluorobenzamide (**198**):

- 10 Compound 198 was prepared according to the method presented for the synthesis of Example 122 substituting ethyl 2,2-difluoroacetate for ethyl 2,2,2-trifluoroacetate to provide 48 mg of title compound: ¹H NMR (400 MHz, cd₃od) δ 8.48 (d, 1H), 7.45 (d, 1H), 7.33 – 7.17 (m, 2H), 7.12 (s, 1H), 7.08 – 6.95 (m, 1H), 6.57 – 6.22 (m, 2H), 6.12 (d, 2H), 5.14 (t, 1H), 4.57 – 4.38 (m, 2H), 2.93 – 2.77 (m, 2H), 2.58 (dd, 1H), 2.44 (dd, 1H), 1.89 (d, 2H), 0.86 (d, 1H), 0.01 (dd, 1H). MS (*m/z*) 582 [M+H]⁺.
- 15

Example 199



Synthesis of 6,6-difluorobicyclo[3.1.0]hexan-3-one (**199A**):

Compound **199A** was prepared according to the method presented in the page 153 of WO 2011/059887 to provide 2.77 g of crude title compound. MS (*m/z*) 133 [M+H]⁺.

5

Synthesis of ethyl 2-(4,4-difluoro-3-(trifluoromethyl)-3b,4,4a,5-tetrahydro-1H-cyclopropa[3,4]cyclopenta[1,2-c]pyrazol-1-yl)acetate (**199C**) and ethyl 2-(5-fluoro-3-(trifluoromethyl)-1H-indazol-1-yl)acetate (**199D**):

Compound **199C** and **199D** were prepared according to the method presented for the synthesis of Example 122 substituting **199A** for **122B** to provide 0.4 g of **199C** and 2 g of **199D**. **199C**: MS (*m/z*) 311 [M+H]⁺ and **199D**: MS (*m/z*) 291 [M+H]⁺.

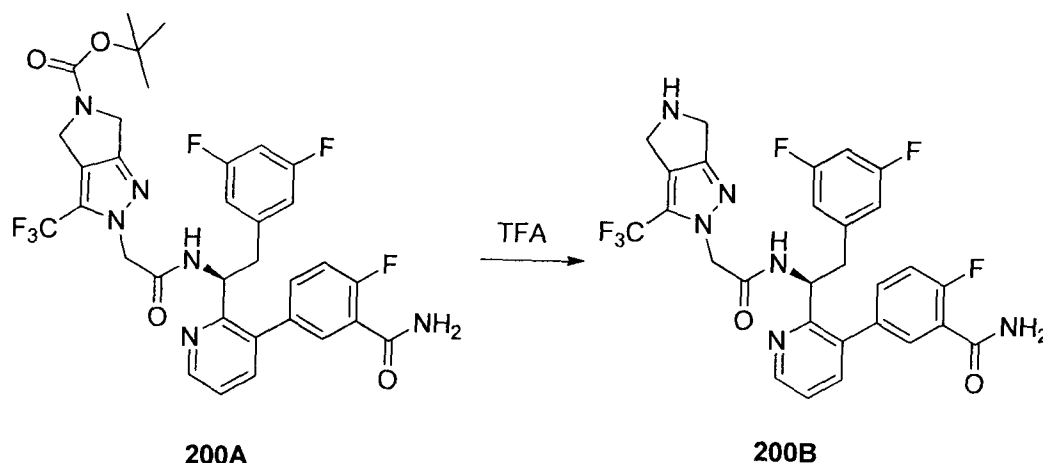
10

Synthesis of 5-(2-((1S)-1-(2-(4,4-difluoro-3-(trifluoromethyl)-3b,4,4a,5-tetrahydro-1H-cyclopropa[3,4]cyclopenta[1,2-c]pyrazol-1-yl)acetamido)-2-(3,5-difluorophenyl)ethyl)pyridin-3-yl)-2-fluorobenzamide (**199E**):

15

Compound 199E was prepared according to the method presented for the synthesis of Example 122 substituting **199C** for **122D** to provide 23 mg of title compound: ^1H NMR (400 MHz, cd_3od) δ 8.70 (d, 1H), 7.65 (dd, 1H), 7.45 (dt, 2H), 7.30 (s, 1H), 7.27 – 7.15 (m, 1H), 6.66 (dd, 1H), 6.32 (t, 2H), 5.34 (t, 1H), 4.82 – 4.70 (m, 2H), 3.15 – 2.93 (m, 5H), 2.85 (dd, 1H). MS (m/z) 636 $[\text{M}+\text{H}]^+$.

Example 200



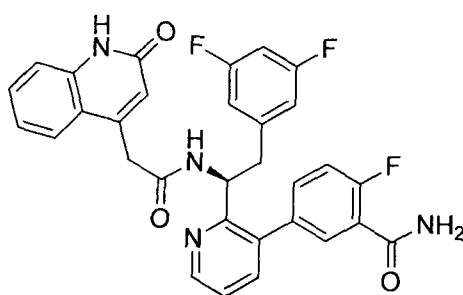
Synthesis of (S)-tert-butyl 2-(2-((1-(3-(3-carbamoyl-4-fluorophenyl)pyridin-2-yl)-2-(3,5-difluorophenyl)ethyl)amino)-2-oxoethyl)-3-(trifluoromethyl)-4,6-dihydropyrrolo[3,4-c]pyrazole-5(2H)-carboxylate (**200A**):

Compound **200A** was prepared according to the method presented for the synthesis of Example 122 substituting 60 mg **190B** for **122D** to provide 35 mg of title compound: MS (m/z) 689 $[\text{M}+\text{H}]^+$.

Synthesis of (S)-5-(2-(2-(3,5-difluorophenyl)-1-(2-(3-(trifluoromethyl)-5,6-dihydropyrrolo[3,4-c]pyrazol-2(4H)-yl)acetamido)ethyl)pyridin-3-yl)-2-fluorobenzamide (**200B**):

200A (35 mg, 0.05 mmol) and trifluoroacetic acid (1 mL) was stirred for 1 hours. Solvents were concentrated *in vacuo* and the residue was purified by RP HPLC using a C18 column with a gradient of H_2O , 0.1% TFA-acetonitrile, to provide 5 mg of title product: ^1H NMR (400 MHz, cd_3od) δ 8.76 – 8.65 (m, 1H), 7.59 (dd, 1H), 7.49 – 7.35 (m, 2H), 7.29 (s, 1H), 7.20 (dd, 1H), 6.67 (t, 1H), 6.35 (d, 2H), 5.34 (t, 1H), 5.00 (s, 2H), 4.51 (s, 2H), 4.43 (s, 2H), 3.06 (ddd, 2H); MS (m/z) 589 $[\text{M}+\text{H}]^+$

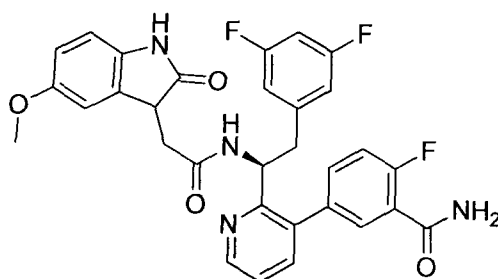
Example 201

**201**

Synthesis of (S)-5-(2-(2-(3,5-difluorophenyl)-1-(2-(2-oxo-1,2-dihydroquinolin-4-yl)acetamido)ethyl)pyridin-3-yl)-2-fluorobenzamide (**201**):

Compound 201 was prepared according to the method presented for the synthesis of Example 54 utilizing **54B** and 2-(2-oxo-1,2-dihydroquinolin-4-yl)acetic acid to provide 83 mg of title compound: ^1H NMR (400 MHz, cd_3od) δ 8.61 (dd, 1H), 7.57 (d, 1H), 7.50 – 7.37 (m, 2H), 7.37 – 7.18 (m, 4H), 7.16 – 7.01 (m, 2H), 6.65 – 6.48 (m, 1H), 6.45 (s, 1H), 6.25 (d, 2H), 5.26 (t, 1H), 3.75 (s, 2H), 3.07 – 2.86 (m, 2H); MS (m/z) 557 [$\text{M}+\text{H}$] $^+$.

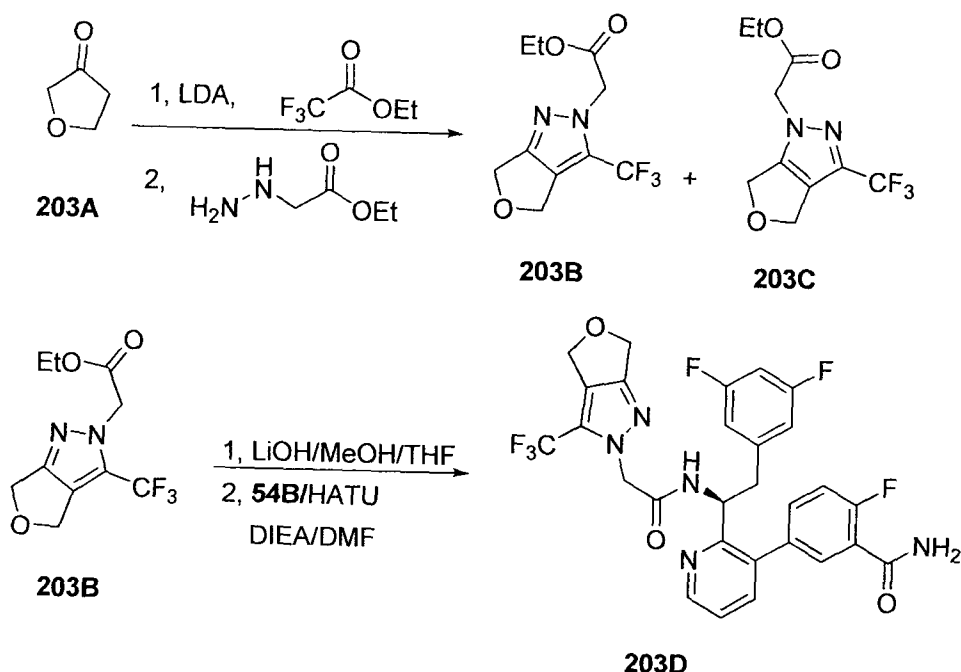
10 Example 202

**202**

Synthesis of 5-(2-((1S)-2-(3,5-difluorophenyl)-1-(2-(5-methoxy-2-oxoindolin-3-yl)acetamido)ethyl)pyridin-3-yl)-2-fluorobenzamide (**202**):

Compound 202 was prepared according to the method presented for the synthesis of Example 54 utilizing **54B** and 2-(5-methoxy-2-oxoindolin-3-yl)acetic acid to provide 17 mg of title compound: ^1H NMR (400 MHz, cd_3od) δ 8.61 (dd, 1H), 7.53 (dd, 1H), 7.43 – 7.34 (m, 1H), 7.29 (dd, 1H), 7.25 – 6.96 (m, 2H), 6.77 – 6.41 (m, 4H), 6.21 (dd, 2H), 5.37 – 5.15 (m, 1H), 3.79 (dt, 1H), 3.61 (d, 3H), 3.10 – 2.81 (m, 2H), 2.69 – 2.48 (m, 2H). MS (m/z) 575 [$\text{M}+\text{H}$] $^+$.

20 Example 203



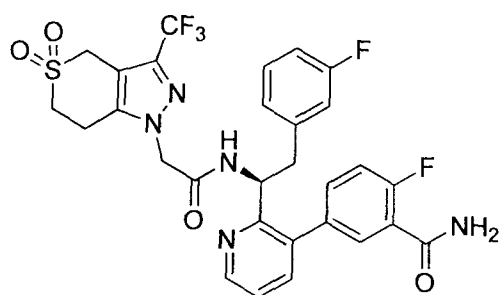
Synthesis of ethyl 2-(3-(trifluoromethyl)-4,6-dihydro-2H-furo[3,4-c]pyrazol-2-yl)acetate (**203B**) and ethyl 2-(3-(trifluoromethyl)-4,6-dihydro-1H-furo[3,4-c]pyrazol-1-yl)acetate (**203C**):

Compound **203B** and **203C** were prepared according to the method presented for the synthesis of Example 122 substituting dihydrofuran-3(2H)-one for **122B** to provide 82 mg of **203B** and 500 mg of **203C**: **203B**: MS (m/z) 265 $[\text{M}+\text{H}]^+$ and **203C**: MS (m/z) 265 $[\text{M}+\text{H}]^+$.

Synthesis of (S)-5-(2-(2-(3,5-difluorophenyl)-1-(2-(3-(trifluoromethyl)-4,6-dihydro-2H-furo[3,4-c]pyrazol-2-yl)acetamido)ethyl)pyridin-3-yl)-2-fluorobenzamide (**203D**):

Compound **203D** was prepared according to the method presented for the synthesis of Example 122 substituting **203B** for **122D** to provide 33 mg of title compound: ^1H NMR (400 MHz, cd_3od) δ 8.75 – 8.67 (m, 1H), 7.63 (dd, 1H), 7.49 – 7.37 (m, 2H), 7.32 (s, 1H), 7.26 – 7.16 (m, 1H), 6.66 (t, 1H), 6.32 (d, 2H), 5.35 (t, 1H), 4.92 (d, 4H), 4.79 (s, 2H), 3.05 (dd, 2H). MS (m/z) 590 $[\text{M}+\text{H}]^+$.

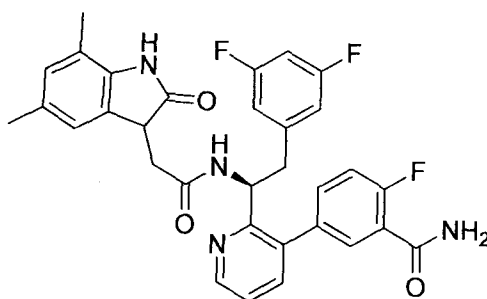
Example 204

**204**

Synthesis of (S)-5-(2-(1-(2-(5,5-dioxido-3-(trifluoromethyl)-6,7-dihydrothiopyrano[4,3-c]pyrazol-1(4H)-yl)acetamido)-2-(3-fluorophenyl)ethyl)pyridin-3-yl)-2-fluorobenzamide (**204**):

Compound 204 was prepared according to the method presented for the synthesis of Example 197 utilizing **228** (62 mg, 0.1 mmol), 3-Chloroperbenzoic acid (87 mg, 77% max., 0.2 mmol) in DCM (3 mL) at 0 °C to provide 39 mg of title compound: ¹H NMR (400 MHz, cd₃od) δ 8.68 (dd, 1H), 7.51 (dd, 1H), 7.42 – 7.31 (m, 2H), 7.15 (t, 2H), 7.05 (td, 1H), 6.81 (td, 1H), 6.52 (d, 1H), 6.43 (d, 1H), 5.40 – 5.28 (m, 1H), 4.87 (d, 2H), 4.32 – 4.17 (m, 2H), 3.44 – 3.24 (m, 4H), 3.24 – 2.95 (m, 4H). MS (*m/z*) 634 [M+H]⁺

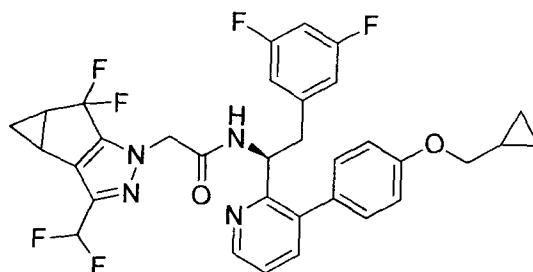
Example 205

**205**

Synthesis of 5-(2-((1S)-2-(3,5-difluorophenyl)-1-(2-(5,7-dimethyl-2-oxoindolin-3-yl)acetamido)ethyl)pyridin-3-yl)-2-fluorobenzamide (**205**):

Compound 205 was prepared according to the method presented for the synthesis of Example 54 utilizing **54B** and 2-(5,7-dimethylindolin-3-yl)acetic acid to provide 19 mg of title compound: ¹H NMR (400 MHz, cd₃od) δ 8.68 (t, 1H), 7.61 (dd, 1H), 7.54 – 7.34 (m, 2H), 7.34 – 7.09 (m, 2H), 6.97 – 6.54 (m, 3H), 6.30 (dd, 2H), 5.37 – 5.24 (m, 1H), 3.83 (dd, 1H), 3.15 – 2.89 (m, 3H), 2.76 – 2.54 (m, 2H), 2.17 (dd, 6H). MS (*m/z*) 573 [M+H]⁺.

Example 206

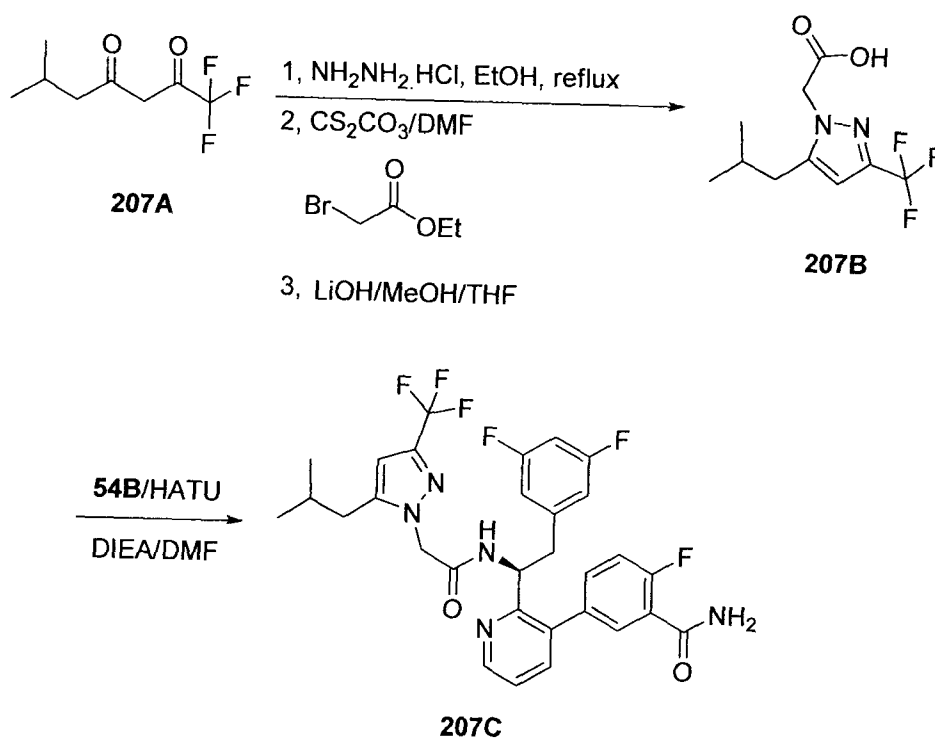
**206**

Synthesis of N-((S)-1-(3-(4-(cyclopropylmethoxy)phenyl)pyridin-2-yl)-2-(3,5-difluorophenyl)ethyl)-2-(3-(difluoromethyl)-5,5-difluoro-3b,4,4a,5-tetrahydro-1H-cyclopropa[3,4]cyclopenta[1,2-c]pyrazol-1-yl)acetamide (**206**):

- 5 Compound 206 was prepared according to the method presented for the synthesis of Example 68 utilizing **68A** and (4-(cyclopropylmethoxy)phenyl)boronic acid to provide 5 mg of title compound: ^1H NMR (400 MHz, cd_3od) δ 8.26 (s, 1H), 7.24 (d, 1H), 7.11 – 7.00 (m, 1H), 6.68 – 6.18 (m, 6H), 5.91 (s, 2H), 5.13 (s, 1H), 3.49 (d, 2H), 2.63 (s, 2H), 2.12 (s, 2H), 1.03 (s, 3H), 0.80 – 0.63 (m, 2H), 0.27 (d, 2H), 0.01 (d, 2H). MS (m/z) 627 $[\text{M}+\text{H}]^+$.

10

Example 207



Synthesis of 2-(5-isobutyl-3-(trifluoromethyl)-1H-pyrazol-1-yl)acetic acid (**207B**):

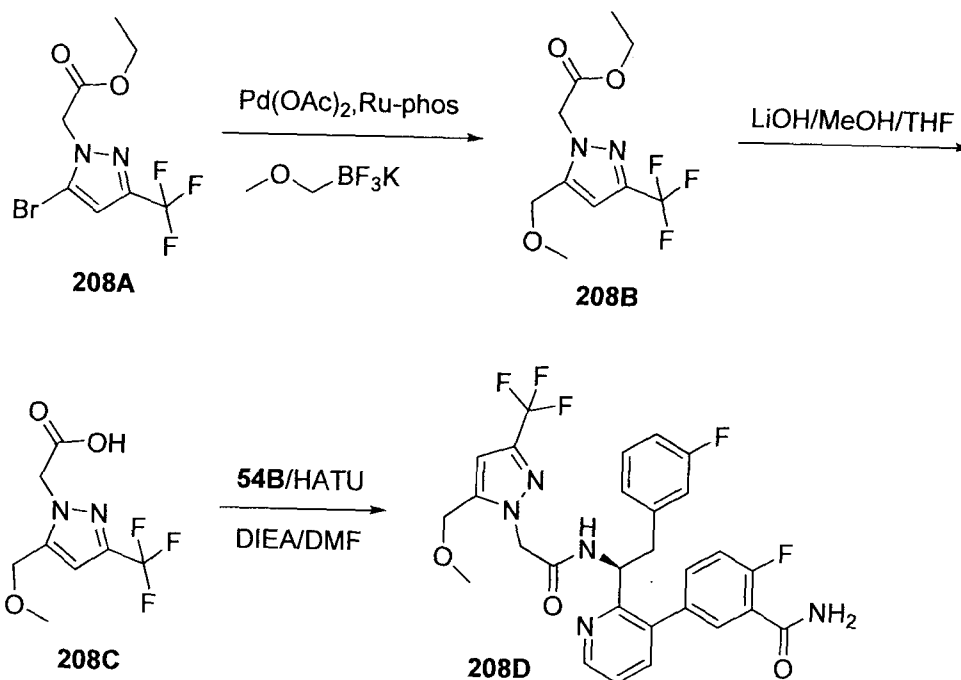
Compound 207B was prepared according to the method presented for the synthesis of Example 238 substituting 1,1,1-trifluoro-6-methylheptane-2,4-dione for **238A** to provide 650 mg of title compound. MS (m/z) 251 $[M+H]^+$.

- 5 Synthesis of (S)-5-(2-(2-(3,5-difluorophenyl)-1-(2-(5-isobutyl-3-(trifluoromethyl)-1H-pyrazol-1-yl)acetamido)ethyl)pyridin-3-yl)-2-fluorobenzamide (**207C**):

Compound 207 was prepared according to the method presented for the synthesis of Example 54 utilizing **54B** and 2-(5-isobutyl-3-(trifluoromethyl)-1H-pyrazol-1-yl)acetic acid to provide 20 mg of title compound: ^1H NMR (400 MHz, cd_3od) δ 8.69 (dd, 1H), 7.63 (dd, 1H), 7.48 – 7.38

- 10 (m, 2H), 7.32 (s, 1H), 7.21 (dd, 1H), 6.67 (dd, 1H), 6.39 (s, 1H), 6.32 (d, 2H), 5.36 (t, 1H), 4.88 (s, 2H), 3.05 (d, 2H), 2.42 (dd, 2H), 1.84 (dt, 1H), 0.88 (dd, 6H). MS (m/z) 604 $[M+H]^+$.

Example 208



15 Synthesis of ethyl 2-(5-bromo-3-(trifluoromethyl)-1H-pyrazol-1-yl)acetate (**208A**):

Compound 208A was prepared according to the method presented for the synthesis of Example 74 substituting 5-bromo-3-(trifluoromethyl)-1H-pyrazole for **74B** to provide 300 mg of title compound. MS (m/z) 300 $[M+H]^+$.

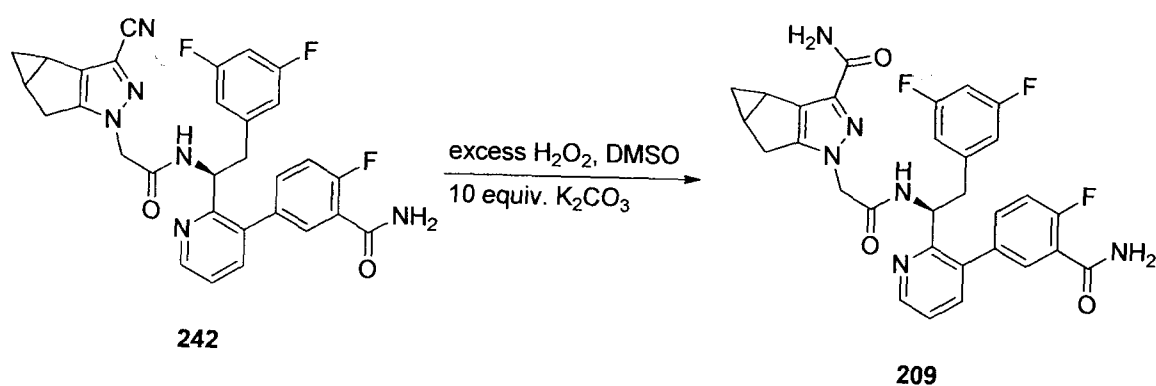
20 Synthesis of ethyl 2-(5-(methoxymethyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl)acetate (**208B**):

To a solution of **208A** (300mg, 0.1mmol) and potassium trifluoro(methoxymethyl)borate (304mg, 0.2 mmol) in 3 ml dioxane/water (10:1) was added 3 aq. Cs_2CO_3 and 2-dicyclohexylphosphino-2',6'-diisopropoxybiphenyl (Ruphos)(93.4mg, 0.2 mmol) and Palladium(II)acetate (22.5 mg, 0.1 mmol). The resulting mixture was heated at reflux for overnight. The reaction mixture was filtered and the mixture was extracted with EtOAc. The organics were dried over Na_2SO_4 , filtered and concentrated. The crude product was purified by SiO_2 chromatography eluting with a gradient of EtOAc in hexanes to provide 12 mg of title compound. MS (m/z) 267 $[\text{M}+\text{H}]^+$.

- 10 Synthesis of 2-(5-(methoxymethyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl)acetic acid (**208C**): Compound 208C was prepared according to the method presented for the synthesis of Example 74 substituting **208B** for **74B** to provide 10 mg of title compound. MS (m/z) 239 $[\text{M}+\text{H}]^+$.

- 15 Synthesis of (S)-2-fluoro-5-(2-(2-(3-fluorophenyl)-1-(2-(5-(methoxymethyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl)acetamido)ethyl)pyridin-3-yl)benzamide (**208D**): Compound 208D was prepared according to the method presented for the synthesis of Example 54 utilizing **54B** and **208D** to provide 3 mg of title compound: ^1H NMR (400 MHz, cd_3od) δ 8.68 (dd, 1H), 7.59 (dd, 1H), 7.40 (dd, 2H), 7.29 (s, 1H), 7.21 (dd, 1H), 6.73 – 6.62 (m, 1H), 6.59 (s, 1H), 6.31 (d, 2H), 5.35 (t, 1H), 4.95 (s, 2H), 4.47 – 4.36 (m, 2H), 3.23 (s, 3H), 3.07 – 3.01 (m, 2H). MS (m/z) 592 $[\text{M}+\text{H}]^+$.
- 20

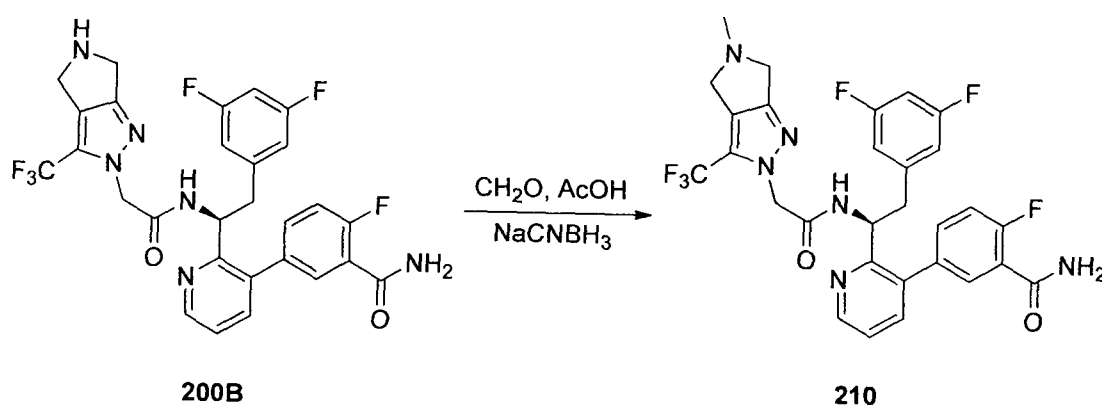
Example 209



Synthesis of 1-(2-(((S)-1-(3-(3-carbamoyl-4-fluorophenyl)pyridin-2-yl)-2-(3,5-difluorophenyl)ethyl)amino)-2-oxoethyl)-3b,4,4a,5-tetrahydro-1H-cyclopropa[3,4]cyclopenta[1,2-c]pyrazole-3-carboxamide (**209**):

H₂O₂ (30 wt %, excess) was added to a suspension of **242** (30 mg, 0.054 mmol) and potassium carbonate (74.5 mg, 0.54 mmol) in DMSO (1 mL) at 0 °C and then stirred for 1 hour. The suspension was filtered and the filtrate was purified by RP HPLC using a C18 column with a gradient of H₂O, 0.1% TFA-acetonitrile, to provide 18 mg of the title compound; ¹H NMR (400 MHz, cd₃od) δ 8.51 (dd, 1H), 7.51 (d, 1H), 7.37 – 7.24 (m, 2H), 7.15 (s, 1H), 7.11 – 6.99 (m, 1H), 6.49 (t, 1H), 6.13 (d, 2H), 5.22 – 5.08 (m, 1H), 4.59 – 4.43 (m, 2H), 2.85 (dd, 2H), 2.66 – 2.53 (m, 1H), 2.50 – 2.39 (m, 1H), 2.04 (s, 1H), 1.87 (s, 1H), 0.88 (dd, 1H), 0.01 (dt, 1H). MS (*m/z*) 575 [M+H]⁺

Example 210



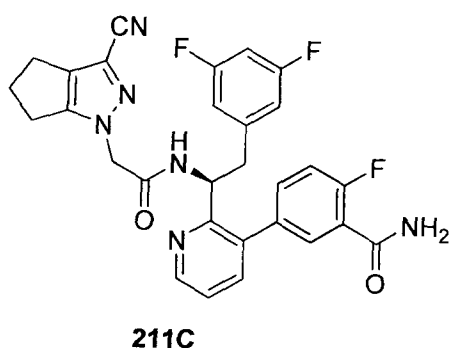
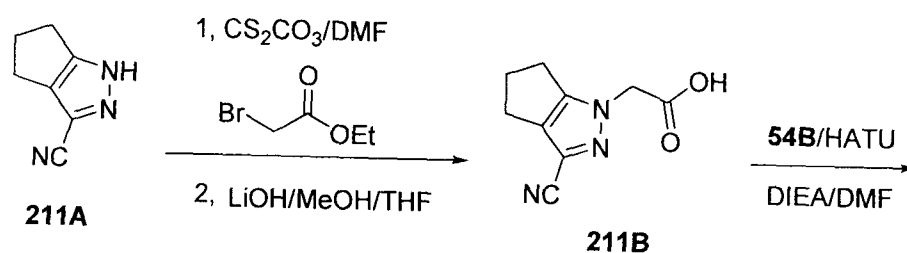
Synthesis of (S)-5-(2-(2-(3,5-difluorophenyl)-1-(2-(5-methyl-3-(trifluoromethyl)-5,6-

dihydropyrrolo[3,4-c]pyrazol-2(4H)-yl)acetamido)ethyl)pyridin-3-yl)-2-fluorobenzamide (**210**):

A mixture of **200B** (30 mg, 0.05 mmol) and formaldehyde (15.3 mg, 0.5 mmol) in acetic acid (1 mL) was stirred for 30 minutes. Sodium cyanoborohydride (4.8 mg, 0.076 mmol) was added to the suspension and stirred for 1 hour. Solvents were concentrated *in vacuo* and the residue was purified by RP HPLC using a C18 column with a gradient of H₂O, 0.1% TFA-acetonitrile, to

provide 18 mg of the title compound: ¹H NMR (400 MHz, cd₃od) δ 8.71 (dd, 1H), 7.59 (dd, 1H), 7.50 – 7.37 (m, 2H), 7.29 (s, 1H), 7.20 (dd, 1H), 6.67 (t, 1H), 6.35 (d, 2H), 5.34 (t, 1H), 5.01 (s, 2H), 4.64 (s, 4H), 3.16 (s, 3H), 3.07 (ddd, 2H); MS (*m/z*) 603 [M+H]⁺

Example 211



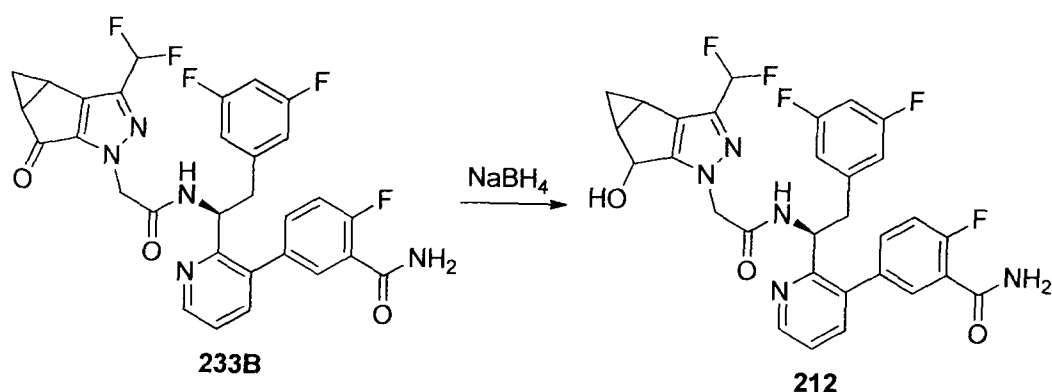
Synthesis of 2-(3-cyano-5,6-dihydrocyclopenta[c]pyrazol-1(4H)-yl)acetic acid (**211B**):

Compound **211B** was prepared according to the method presented for the synthesis of Example 74 substituting 1,4,5,6-tetrahydrocyclopenta[c]pyrazole-3-carbonitrile (**211A**) for 1-7,8,8-trimethyl-3-(trifluoromethyl)-4,5,6,7-tetrahydro-1H-4,7-methanoindazole (**74A**) to provide 300 mg of title compound: MS (m/z) 192 $[\text{M}+\text{H}]^+$.

Synthesis of (S)-5-(2-(1-(2-(3-cyano-5,6-dihydrocyclopenta[c]pyrazol-1(4H)-yl)acetamido)-2-(3,5-difluorophenyl)ethyl)pyridin-3-yl)-2-fluorobenzamide (**211C**):

Compound **211C** was prepared according to the method presented for the synthesis of Example 54 utilizing **54B** and 2-(3-cyano-5,6-dihydrocyclopenta[c]pyrazol-1(4H)-yl)acetic acid (**211B**) to provide 42 mg of title compound: ^1H NMR (400 MHz, cd_3od) δ 8.71 (dd, 1H), 7.67 (dd, 1H), 7.47 (dd, 2H), 7.33 (s, 1H), 7.23 (dd, 1H), 6.67 (t, 1H), 6.33 (d, 2H), 5.35 (t, 1H), 4.81 (s, 2H), 3.06 (d, 2H), 2.77 – 2.48 (m, 6H). MS (m/z) 545 $[\text{M}+\text{H}]^+$.

Example 212

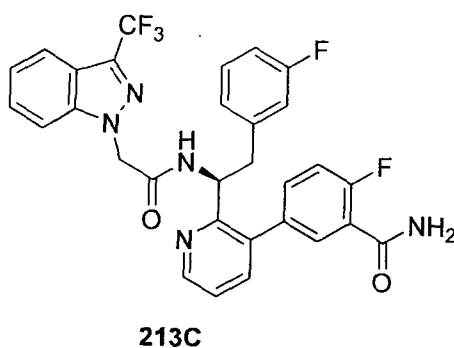
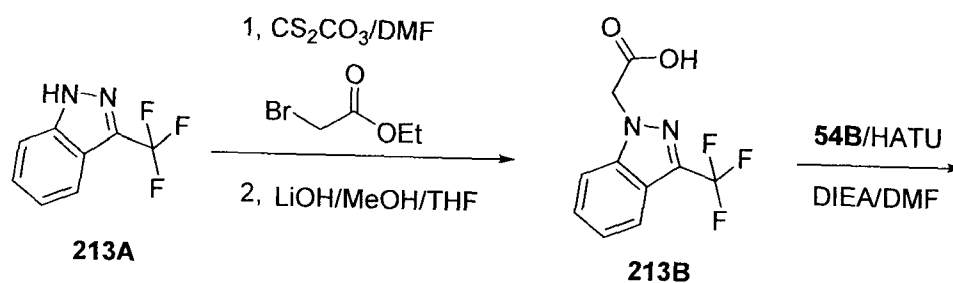


Synthesis of 5-(2-((1S)-1-(2-(3-(difluoromethyl)-5-hydroxy-3b,4,4a,5-tetrahydro-1H-cyclopropa[3,4]cyclopenta[1,2-c]pyrazol-1-yl)acetamido)-2-(3,5-difluorophenyl)ethyl)pyridin-3-yl)-2-fluorobenzamide (**212**):

- 5 Compound 212 was prepared according to the method presented for the synthesis of Example 154 substituting **233B** for **154B** to provide 12 mg of title compound: ^1H NMR (400 MHz, cd_3od) δ 8.61 (dd, 1H), 7.57 (d, 1H), 7.37 (dd, 2H), 7.28 – 7.08 (m, 2H), 6.78 – 6.34 (m, 2H), 6.32 – 6.14 (m, 2H), 5.39 – 5.17 (m, 2H), 4.66 (ddd, 2H), 3.04 – 2.88 (m, 2H), 2.19 – 1.99 (m, 2H), 0.95 – 0.65 (m, 2H). MS (m/z) 598 $[\text{M}+\text{H}]^+$.

10

Example 213



Synthesis of 2-(3-(trifluoromethyl)-1H-indazol-1-yl)acetic acid (**213B**):

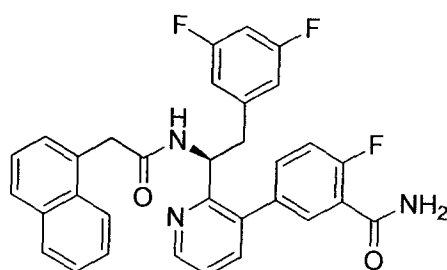
- 15 Compound 213B was prepared according to the method presented for the synthesis of Example 74 substituting 3-(trifluoromethyl)-1H-indazole (**213A**) for 1-7,8,8-trimethyl-3-

(trifluoromethyl)-4,5,6,7-tetrahydro-1H-4,7-methanoindazole (**74A**) to provide 155 mg of title compound. MS (m/z) 245 $[M+H]^+$.

Synthesis of (S)-2-fluoro-5-(2-(2-(3-fluorophenyl)-1-(2-(3-(trifluoromethyl)-1H-indazol-1-yl)acetamido)ethyl)pyridin-3-yl)benzamide (**213B**):

Compound 213 was prepared according to the method presented for the synthesis of Example 59 utilizing **59D** and 2-(3-(trifluoromethyl)-1H-indazol-1-yl)acetic acid (**213B**) to provide 25 mg of title compound: ^1H NMR (400 MHz, cd_3od) δ 8.70 (dd, 1H), 7.78 (d, 1H), 7.63 (dd, 1H), 7.59 – 7.41 (m, 3H), 7.38 – 7.11 (m, 4H), 7.04 (dd, 1H), 6.82 (t, 1H), 6.47 (dd, 2H), 5.34 (t, 1H), 5.23 (s, 2H), 3.07 (d, 2H). MS (m/z) 580 $[M+H]^+$.

Example 214

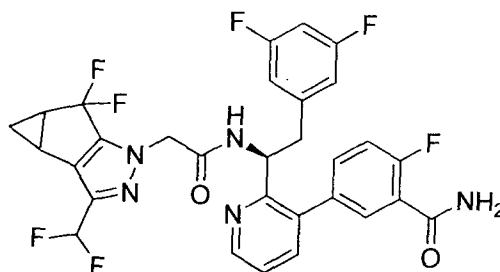


214

Synthesis of (S)-5-(2-(2-(3,5-difluorophenyl)-1-(2-(naphthalen-1-yl)acetamido)ethyl)pyridin-3-yl)-2-fluorobenzamide (**214**):

Compound 214 was prepared according to the method presented for the synthesis of Example 54 utilizing **54B** and 2-(naphthalen-1-yl)acetic acid to provide: ^1H NMR (400 MHz, cdcl_3) δ 8.76 (d, 1H), 8.69 (d, 1H), 7.94 (d, 1H), 7.80 (dd, 3H), 7.72 – 7.66 (m, 1H), 7.61 (d, 1H), 7.49 – 7.34 (m, 3H), 7.34 – 7.25 (m, 1H), 6.99 (d, 1H), 6.10 (d, 2H), 5.39 (dd, 1H), 4.01 (p, 2H), 2.99 (ddd, 2H). MS (m/z) 540 $[M+H]^+$.

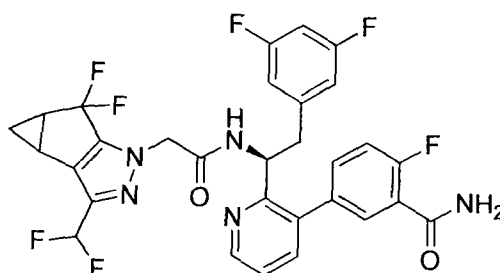
Example 215

**215**

Synthesis of 5-(2-((1S)-1-(2-(3-(difluoromethyl)-5,5-difluoro-3b,4,4a,5-tetrahydro-1H-cyclopropa[3,4]cyclopenta[1,2-c]pyrazol-1-yl)acetamido)-2-(3,5-difluorophenyl)ethyl)pyridin-3-yl)-2-fluorobenzamide (**215**):

- 5 **215** was separated from the diastereomeric mixture of **60** by semi-preparative chiral HPLC fitted with a Chiralcel AZ-H column running a 70:30 mixture of Hep:IPA. The fast eluent was collected to obtain 58 mg of the single diastereomer: ^1H NMR (400 MHz, cd_3od) δ 8.65 (dd, 1H), 7.53 (dd, 1H), 7.35 (dd, 2H), 7.33 – 7.12 (m, 2H), 6.87 – 6.48 (m, 2H), 6.26 (d, 2H), 5.40 – 5.28 (m, 1H), 4.79 (s, 2H), 3.00 (qd, 2H), 2.51 – 2.36 (m, 2H), 1.16 – 1.08 (m, 1H), 1.02 (d, 1H).
- 10 MS (m/z) 618 $[\text{M}+\text{H}]^+$.

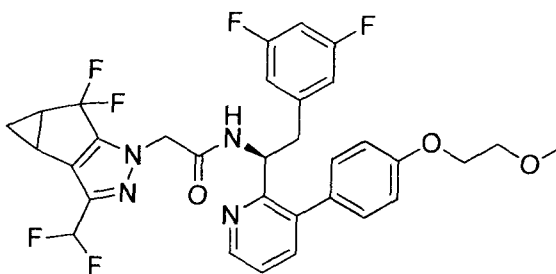
Example 216

**216**

Synthesis of 5-(2-((1S)-1-(2-(3-(difluoromethyl)-5,5-difluoro-3b,4,4a,5-tetrahydro-1H-cyclopropa[3,4]cyclopenta[1,2-c]pyrazol-1-yl)acetamido)-2-(3,5-difluorophenyl)ethyl)pyridin-3-yl)-2-fluorobenzamide (**216**):

- 216** was separated from the diastereomeric mixture of **60** by semi-preparative chiral HPLC fitted with a Chiralcel AZ-H column running a 70:30 mixture of Hep:IPA. The slow eluent was collected to obtain 58 mg of the single diastereomer: ^1H NMR (400 MHz, cd_3od) δ 8.66 (dd, 1H), 7.52 (dd, 1H), 7.35 (dd, 2H), 7.31 – 7.13 (m, 2H), 6.83 – 6.48 (m, 2H), 6.26 (d, 2H), 5.40 – 5.26 (m, 1H), 4.79 (s, 2H), 3.12 – 2.93 (m, 2H), 2.44 (ddd, 2H), 1.18 – 1.10 (m, 1H), 1.10 – 1.00 (m, 1H). MS (m/z) 618 $[\text{M}+\text{H}]^+$.

Example 217

**217**

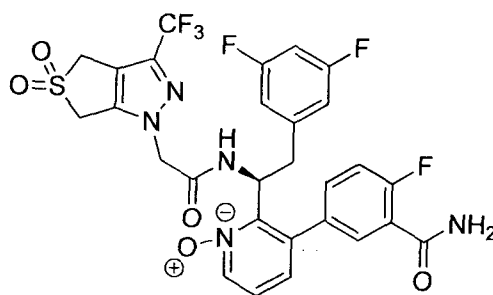
Synthesis of 2-(3-(difluoromethyl)-5,5-difluoro-3b,4,4a,5-tetrahydro-1H-

5 cyclopropa[3,4]cyclopenta[1,2-c]pyrazol-1-yl)-N-((S)-2-(3,5-difluorophenyl)-1-(3-(4-(2-methoxyethoxy)phenyl)pyridin-2-yl)ethyl)acetamide (**217**):

Compound 217 was prepared according to the method presented for the synthesis of Example 68 utilizing **68A** and (4-(2-methoxyethoxy)phenyl)boronic acid to provide 8 mg of title compound:

¹H NMR (400 MHz, cd₃od) δ 8.61 (d, 1H), 7.61 (d, 1H), 7.41 (dd, 1H), 7.07 – 6.87 (m, 4H), 6.68 (ddd, 2H), 6.25 (d, 2H), 5.48 (d, 1H), 4.13 (d, 2H), 3.81 – 3.70 (m, 2H), 3.42 (s, 3H), 2.96 (dd, 2H), 2.46 (s, 2H), 1.37 (s, 1H), 1.07 (s, 1H). MS (*m/z*) 631 [M+H]⁺.

Example 218

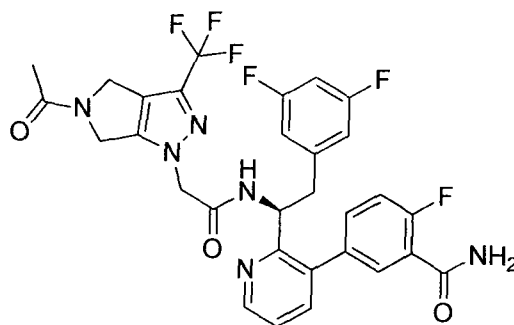
**218**

Synthesis of (S)-3-(3-carbamoyl-4-fluorophenyl)-2-(2-(3,5-difluorophenyl)-1-(2-(5,5-dioxido-3-(trifluoromethyl)-4,6-dihydro-1H-thieno[3,4-c]pyrazol-1-yl)acetamido)ethyl)pyridine 1-oxide (**218**):

20 Compound 218 was prepared according to the method presented for the synthesis of Example 197 utilizing **189** to provide 25 mg of title compound: ¹H NMR (400 MHz, cd₃od) δ 8.32 (d, 1H), 7.85 (dd, 1H), 7.54 – 7.44 (m, 1H), 7.44 – 7.28 (m, 2H), 7.21 (d, 1H), 7.18 – 7.07 (m, 1H),

6.62 (t, 1H), 6.33 (d, 2H), 5.48 – 5.31 (m, 1H), 5.03 – 4.85 (m, 2H), 4.42 – 4.17 (m, 3H), 3.51 (dd, 1H), 3.04 (dd, 1H). MS (m/z) 654 $[M+H]^+$

Example 219

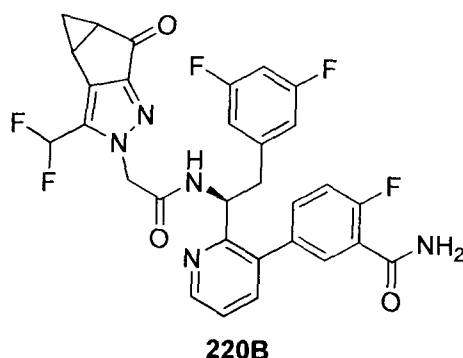
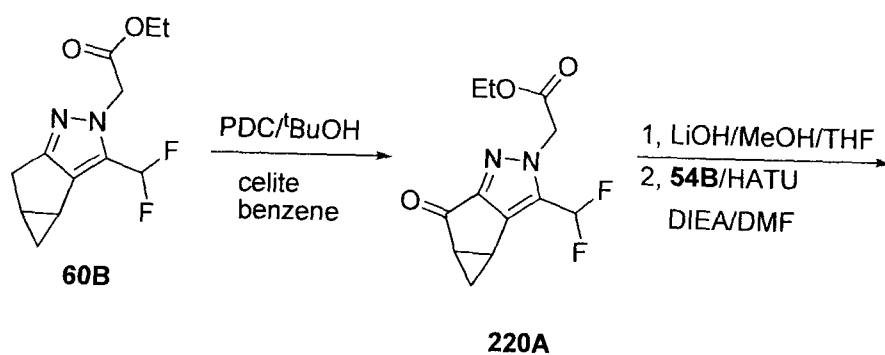


219

Synthesis of (S)-5-(2-(1-(2-(5-acetyl-3-(trifluoromethyl)-5,6-dihydropyrrolo[3,4-c]pyrazol-1(4H)-yl)acetamido)-2-(3,5-difluorophenyl)ethyl)pyridin-3-yl)-2-fluorobenzamide (**219**):

Compound 219 was prepared according to the method presented for the synthesis of Example 54 substituting **251** for **54B** to provide 32 mg of title compound: ^1H NMR (400 MHz, cd_3od) δ 8.75 – 8.67 (m, 1H), 7.64 (d, 1H), 7.58 – 7.40 (m, 2H), 7.25 (dd, 2H), 6.66 (t, 1H), 6.32 (d, 2H), 5.35 (dd, 1H), 4.92 (d, 2H), 4.69 (d, 2H), 4.51 (d, 2H), 3.16 – 3.01 (m, 2H), 2.11 (d, 3H). MS (m/z) 631 $[M+H]^+$.

Example 220



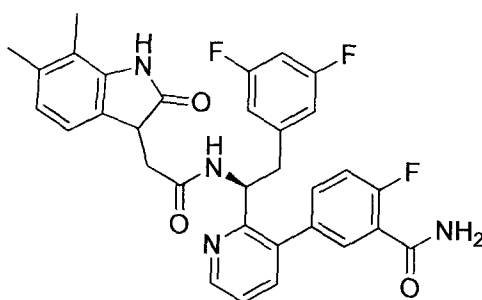
Synthesis of 2-(3-(difluoromethyl)-5-oxo-3b,4,4a,5-tetrahydro-2H-cyclopropa[3,4]cyclopenta[1,2-c]pyrazol-2-yl)acetic acid (**220A**):

Compound 220A was prepared according to the method presented for the synthesis of Example 181 substituting **60B** for **122D** to provide 8 mg of title compound. MS (m/z) 271 [$M+H$]⁺.

Synthesis of 5-(2-((1S)-1-(2-(3-(difluoromethyl)-5-oxo-3b,4,4a,5-tetrahydro-2H-cyclopropa[3,4]cyclopenta[1,2-c]pyrazol-2-yl)acetamido)-2-(3,5-difluorophenyl)ethyl)pyridin-3-yl)-2-fluorobenzamide (**220B**):

Compound 220B was prepared according to the method presented for the synthesis of Example 154 substituting **220A** for **181A** to provide 6 mg of title compound: ¹H NMR (400 MHz, cd_3od) δ 8.62 (dd, 1H), 7.54 (dd, 1H), 7.35 (dd, 2H), 7.15 (dd, 2H), 6.90 (td, 1H), 6.58 (t, 1H), 6.22 (d, 2H), 5.26 (t, 1H), 4.94 (s, 2H), 3.05 – 2.89 (m, 2H), 2.78 – 2.67 (m, 1H), 2.50 – 2.38 (m, 1H), 1.58 (dd, 1H), 1.40 (dd, 1H). MS (m/z) 596 [$M+H$]⁺.

Example 221

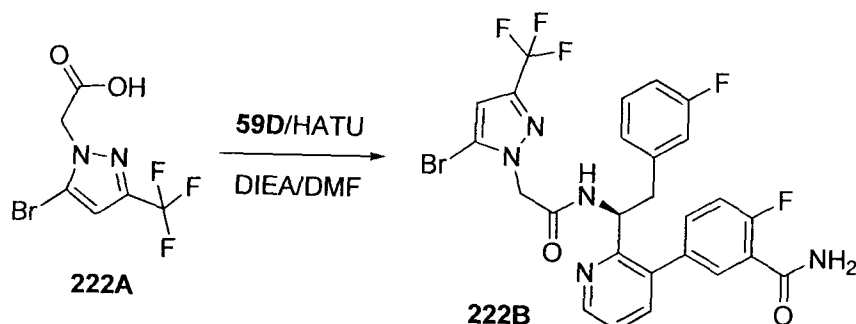
**221**

Synthesis of 5-(2-((1S)-2-(3,5-difluorophenyl)-1-(2-(6,7-dimethyl-2-oxoindolin-3-yl)acetamido)ethyl)pyridin-3-yl)-2-fluorobenzamide (**221**):

Compound **221** was prepared according to the method presented for the synthesis of Example 54 utilizing **54B** and 2-(6,7-dimethylindolin-3-yl)acetic acid to provide 15 mg of title compound:

^1H NMR (400 MHz, cd_3od) δ 8.64 (td, 1H), 7.71 – 7.56 (m, 1H), 7.49 – 7.40 (m, 1H), 7.40 – 6.91 (m, 3H), 6.76 (dd, 1H), 6.66 – 6.49 (m, 2H), 6.49 – 6.10 (m, 3H), 5.22 (dd, 1H), 3.61 (dd, 1H), 2.99 – 2.47 (m, 5H), 2.22 – 1.94 (m, 6H). MS (m/z) 573 $[\text{M}+\text{H}]^+$.

10 Example 222



Synthesis of 2-(5-bromo-3-(trifluoromethyl)-1H-pyrazol-1-yl)acetic acid (**222A**):

Compound **222A** was prepared according to the method presented for the synthesis of Example 74 substituting 5-bromo-3-(trifluoromethyl)-1H-pyrazole for **74B** to provide 270 mg of title compound. MS (m/z) 273 $[\text{M}+\text{H}]^+$.

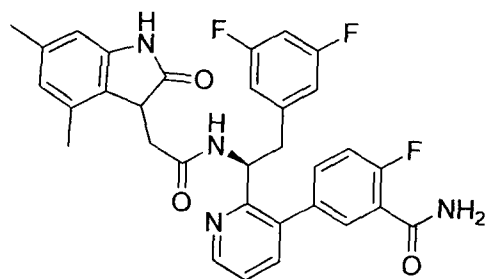
Synthesis of (S)-5-(2-(1-(2-(5-bromo-3-(trifluoromethyl)-1H-pyrazol-1-yl)acetamido)-2-(3-fluorophenyl)ethyl)pyridin-3-yl)-2-fluorobenzamide (**222B**):

Compound **222B** was prepared according to the method presented for the synthesis of Example 59 utilizing **59D** and 2-(5-bromo-3-(trifluoromethyl)-1H-pyrazol-1-yl)acetic acid (**222A**) to provide 490 mg of title compound: ^1H NMR (400 MHz, cd_3od) δ 8.62 (dd, 1H), 7.54 (dd, 1H), 7.35 (dd, 2H), 7.15 (dd, 2H), 6.90 (td, 1H), 6.58 (t, 1H), 6.22 (d, 2H), 5.26 (t, 1H), 4.94 (s, 2H),

3.05 – 2.89 (m, 2H), 2.78 – 2.67 (m, 1H), 2.50 – 2.38 (m, 1H), 1.58 (dd, 1H), 1.40 (dd, 1H).MS (m/z) 608 $[M+H]^+$.

Example 223

5

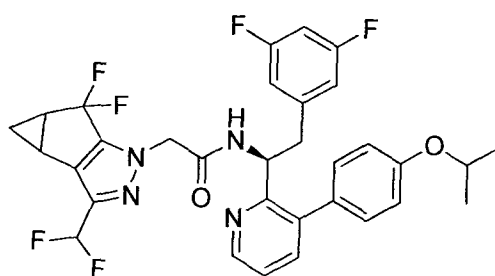


223

Synthesis of 5-(2-((1S)-2-(3,5-difluorophenyl)-1-(2-(5,7-dimethyl-2-oxoindolin-3-yl)acetamido)ethyl)pyridin-3-yl)-2-fluorobenzamide (**223**):

Compound **223** was prepared according to the method presented for the synthesis of Example 54 utilizing **54B** and 2-(5,7-dimethylindolin-3-yl)acetic acid to provide 19 mg of title compound: ^1H NMR (400 MHz, cd_3od) δ 8.70 – 8.54 (m, 1H), 7.76 – 7.52 (m, 1H), 7.33 (dddd, 4H), 6.79 – 6.46 (m, 3H), 6.27 (dd, 2H), 5.39 – 5.21 (m, 1H), 4.04 (dd, 2H), 3.07 – 2.56 (m, 5H), 2.31 – 2.09 (m, 6H).MS (m/z) 573 $[M+H]^+$.

Example 224



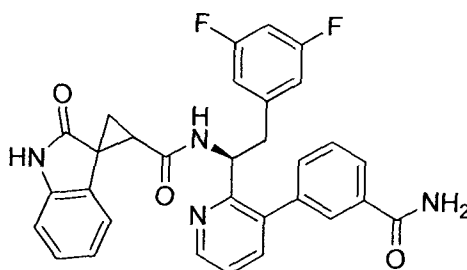
224

Synthesis of 2-(3-(difluoromethyl)-5,5-difluoro-3b,4,4a,5-tetrahydro-1H-cyclopropa[3,4]cyclopenta[1,2-c]pyrazol-1-yl)-N-((S)-2-(3,5-difluorophenyl)-1-(3-(4-isopropoxyphenyl)pyridin-2-yl)ethyl)acetamide (**224**):

Compound **224** was prepared according to the method presented for the synthesis of Example 68 utilizing **68A** and (4-isopropoxyphenyl)boronic acid to provide 14 mg of title compound: ^1H NMR (400 MHz, cd_3od) δ 8.61 (d, 1H), 7.64 (d, 1H), 7.43 (dd, 1H), 7.04 – 6.95 (m, 2H), 6.89

(dd, 2H), 6.68 (ddd, 2H), 6.26 (s, 2H), 5.50 (d, 1H), 4.69 – 4.56 (m, 1H), 2.96 (t, 2H), 2.46 (s, 2H), 1.46 – 1.21 (m, 7H), 1.02 (s, 1H). MS (m/z) 615 $[M+H]^+$.

Example 225

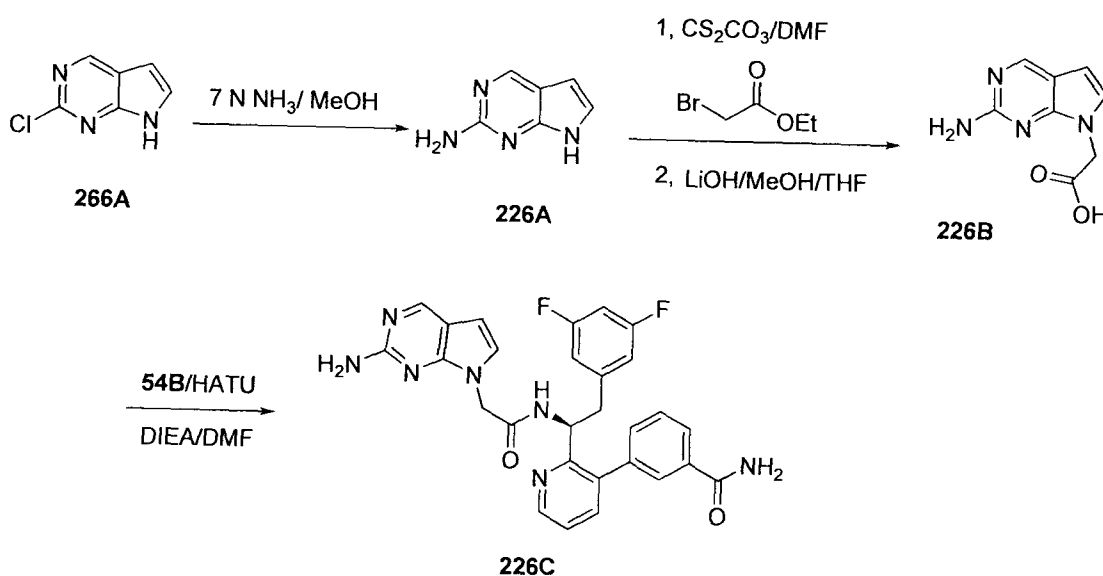


225

Synthesis of N-((S)-1-(3-(3-carbamoylphenyl)pyridin-2-yl)-2-(3,5-difluorophenyl)ethyl)-2'-oxospiro[cyclopropane-1,3'-indoline]-2-carboxamide (**225**):

Compound **225** was prepared according to the method presented for the synthesis of Example 50 utilizing **50C** and 2'-oxospiro[cyclopropane-1,3'-indoline]-2-carboxylic acid to provide 46 mg of title compound: ^1H NMR (400 MHz, dmso) δ 10.56 (d, 1H), 8.91 (dd, 1H), 8.50 (dd, 1H), 8.06 – 7.85 (m, 2H), 7.78 – 7.21 (m, 6H), 7.12 – 6.56 (m, 5H), 6.50 (d, 1H), 6.18 (d, 1H), 5.17 (dd, 1H), 2.94 (d, 1H), 2.86 – 2.71 (m, 1H), 2.63 (t, 1H), 1.88 – 1.76 (m, 1H), 1.61 – 1.50 (m, 1H). MS (m/z) 539 $[M+H]^+$.

Example 226



Synthesis of 7H-pyrrolo[2,3-d]pyrimidin-2-amine (**226A**):

A solution of **266A** in 10 mL of NH_3 (7N in MeOH) was heated at 130 °C in sealed tube overnight. The reaction was monitored by LC/Mass until completion. Remove the solvent and used as crude. MS (m/z) 135 $[\text{M}+\text{H}]^+$.

5 Synthesis of 2 ethyl 2-(2-amino-7H-pyrrolo[2,3-d]pyrimidin-7-yl)acetate (**226B**):

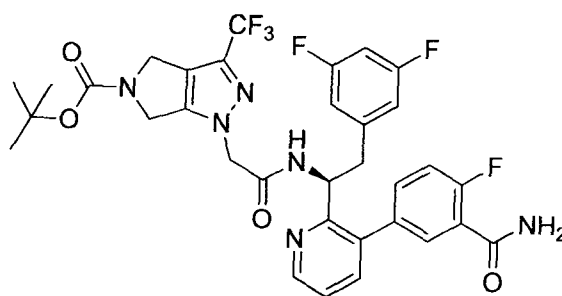
Compound 266B was prepared according to the method presented for the synthesis of Example 74 substituting 7H-pyrrolo[2,3-d]pyrimidin-2-amine (**226A**) for 1 7,8,8-trimethyl-3-(trifluoromethyl)-4,5,6,7-tetrahydro-1H-4,7-methanoindazole (**74A**) to provide 20 mg of title compound. MS (m/z) 221 $[\text{M}+\text{H}]^+$.

10

Synthesis of (S)-3-(2-(1-(2-(2-amino-7H-pyrrolo[2,3-d]pyrimidin-7-yl)acetamido)-2-(3,5-difluorophenyl)ethyl)pyridin-3-yl)benzamide (**226C**):

Compound 226C was prepared according to the method presented for the synthesis of Example 50 utilizing **50C** and 2-(2-amino-7H-pyrrolo[2,3-d]pyrimidin-7-yl)acetic (**226B**) to provide 15
 15 mg of title compound: ^1H NMR (400 MHz, cd_3od) δ 8.64 – 8.54 (m, 1H), 8.40 (s, 1H), 7.77 (d, 1H), 7.56 – 7.45 (m, 2H), 7.37 (t, 1H), 7.30 (dd, 1H), 7.15 (d, 1H), 7.06 (d, 1H), 6.55 (t, 1H), 6.43 (d, 1H), 6.15 (d, 2H), 5.44 – 5.31 (m, 3H), 2.93 (ddd, 2H). MS (m/z) 528 $[\text{M}+\text{H}]^+$.

Example 227



227

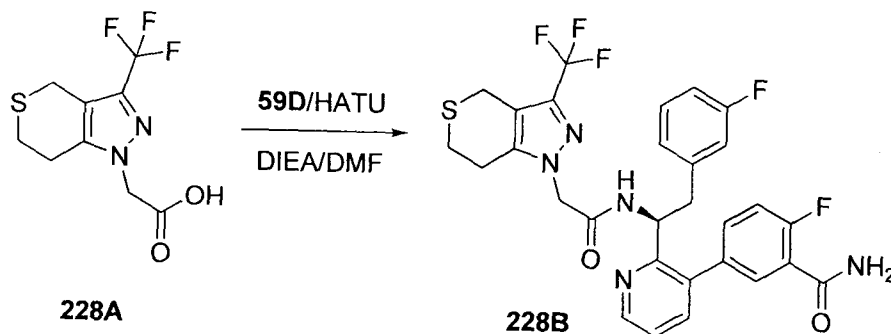
20

Synthesis of (S)-tert-butyl 1-(2-((1-(3-(3-carbamoyl-4-fluorophenyl)pyridin-2-yl)-2-(3,5-difluorophenyl)ethyl)amino)-2-oxoethyl)-3-(trifluoromethyl)-4,6-dihydropyrrolo[3,4-c]pyrazole-5(1H)-carboxylate (**227**):

Compound 227 was prepared according to the method presented for the synthesis of

25 Example 122 substituting **190D** for **122D** to provide 40 mg of title compound: ^1H NMR (400 MHz, cd_3od) δ 8.70 (s, 1H), 7.65 (d, 1H), 7.51 – 7.18 (m, 4H), 6.65 (s, 1H), 6.32 (s, 2H), 5.35 (d, 1H), 4.89 (d, 2H), 4.43 (d, 4H), 3.06 (d, 2H), 1.49 (d, 9H). MS (m/z) 689 $[\text{M}+\text{H}]^+$.

Example 228



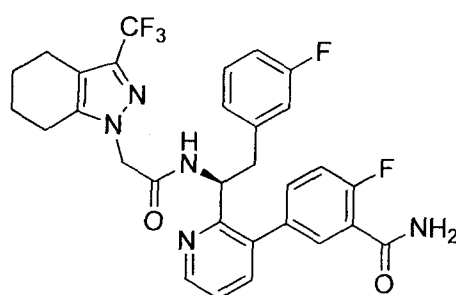
Synthesis of 2-(3-(trifluoromethyl)-6,7-dihydrothiopyrano[4,3-c]pyrazol-1(4H)-yl)acetic acid (**228A**):

- 5 Compound **228A** was prepared according to the method presented for the synthesis of Example 122 substituting dihydro-2H-thiopyran-4(3H)-one for **122B** to provide 1 g of title compound. MS (m/z) 267 $[M+H]^+$.

Synthesis of (S)-2-fluoro-5-(2-(2-(3-fluorophenyl)-1-(2-(3-(trifluoromethyl)-6,7-

- 10 dihydrothiopyrano[4,3-c]pyrazol-1(4H)-yl)acetamido)ethyl)pyridin-3-yl)benzamide (**228B**): Compound **228B** was prepared according to the method presented for the synthesis of Example 59 utilizing **59D** and **228A** to provide 27 mg of title compound: ^1H NMR (400 MHz, cd_3od) δ 8.72 (dd, 1H), 7.70 (dd, 1H), 7.50 (dd, 1H), 7.38 (d, 1H), 7.28 (s, 1H), 7.20 (dd, 1H), 7.07 (dd, 1H), 6.84 (td, 1H), 6.50 (dd, 2H), 5.33 (dd, 1H), 3.65 (d, 2H), 3.12 – 3.01 (m, 2H), 2.87 (dd, 15 2H), 2.77 – 2.66 (m, 2H). MS (m/z) 602 $[M+H]^+$.

Example 229

**229**

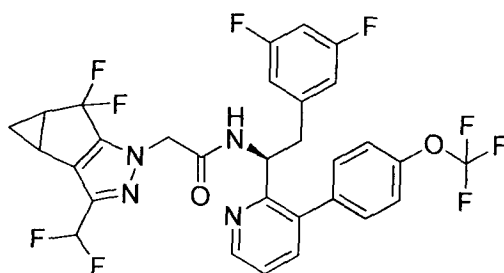
- 20 Synthesis of (S)-2-fluoro-5-(2-(2-(3-fluorophenyl)-1-(2-(3-(trifluoromethyl)-4,5,6,7-tetrahydro-1H-indazol-1-yl)acetamido)ethyl)pyridin-3-yl)benzamide (**229**):

Compound **229** was prepared according to the method presented for the synthesis of Example 59 utilizing **59D** and 2-(3-(trifluoromethyl)-4,5,6,7-tetrahydro-1H-indazol-1-yl)acetic acid to

provide 37 mg of title compound: ^1H NMR (400 MHz, cd_3od) δ 8.70 (dd, 1H), 7.66 (dd, 1H), 7.47 (dd, 1H), 7.36 (d, 1H), 7.25 (d, 1H), 7.20 – 7.14 (m, 1H), 7.07 (dd, 1H), 6.83 (dd, 1H), 6.49 (dd, 2H), 5.35 (t, 1H), 4.78 (s, 2H), 3.05 (d, 2H), 2.54 (t, 2H), 2.44 (s, 2H), 1.75 (dd, 4H). MS (m/z) 584 $[\text{M}+\text{H}]^+$.

5

Example 230



230

Synthesis of 2-(3-(difluoromethyl)-5,5-difluoro-3b,4,4a,5-tetrahydro-1H-cyclopropa[3,4]cyclopenta[1,2-c]pyrazol-1-yl)-N-((S)-2-(3,5-difluorophenyl)-1-(3-(4-(trifluoromethoxy)phenyl)pyridin-2-yl)ethyl)acetamide (**230**):

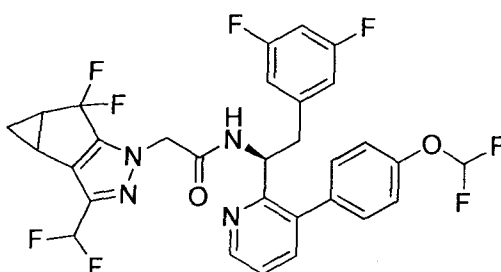
10

Compound 230 was prepared according to the method presented for the synthesis of Example 68 utilizing **68A** and (4-(trifluoromethoxy)phenyl)boronic acid to provide 13 mg of title compound:

^1H NMR (400 MHz, cd_3od) δ 8.67 (d, 1H), 7.58 (d, 1H), 7.40 (dd, 1H), 7.24 (s, 2H), 7.18 – 7.08 (m, 2H), 6.68 (ddd, 2H), 6.23 (d, 2H), 5.38 (d, 1H), 2.99 (t, 2H), 2.46 (s, 2H), 1.37 (s, 1H), 1.03 (s, 1H). MS (m/z) 641 $[\text{M}+\text{H}]^+$.

15

Example 231



231

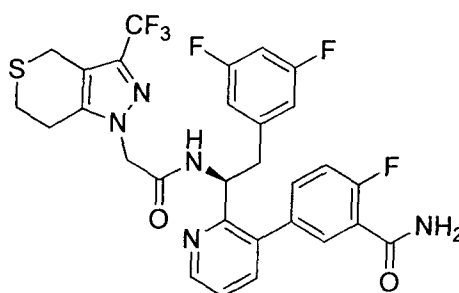
Synthesis of N-((S)-1-(3-(4-(difluoromethoxy)phenyl)pyridin-2-yl)-2-(3,5-difluorophenyl)ethyl)-2-(3-(difluoromethyl)-5,5-difluoro-3b,4,4a,5-tetrahydro-1H-cyclopropa[3,4]cyclopenta[1,2-c]pyrazol-1-yl)acetamide (**231**):

20

Compound 231 was prepared according to the method presented for the synthesis of Example 68 utilizing **68A** and (4-(difluoromethoxy)phenyl)boronic acid to provide 4 mg of title compound:

¹H NMR (400 MHz, cd₃od) δ 8.65 (d, 1H), 7.58 (d, 1H), 7.39 (dd, 1H), 7.09 (dd, 4H), 7.04 – 6.50 (m, 4H), 6.27 (s, 2H), 5.40 (s, 1H), 2.99 (d, 2H), 2.46 (s, 2H), 1.37 (s, 1H), 1.10 – 1.02 (m, 1H). MS (*m/z*) 641 [M+H]⁺.

Example 232

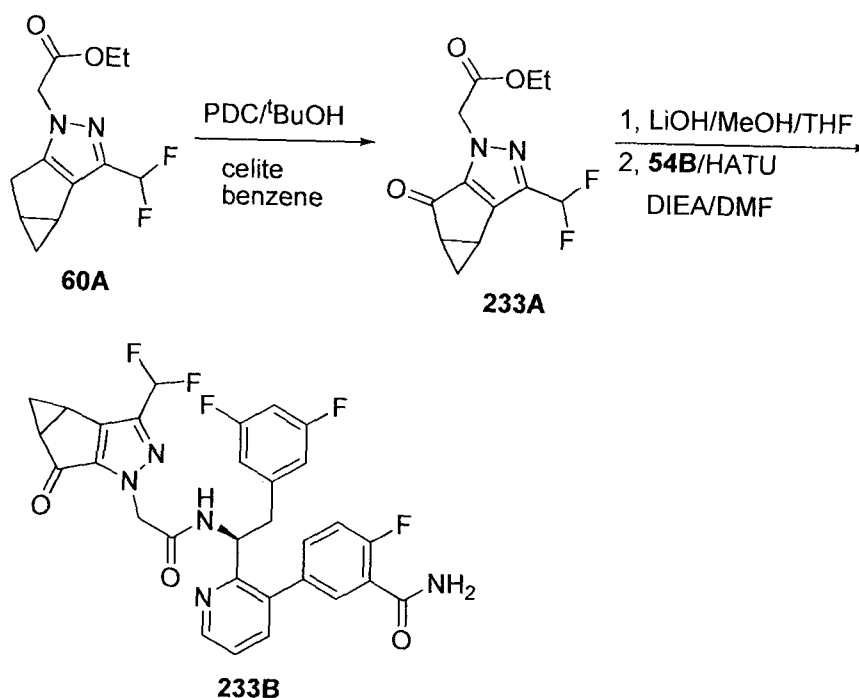


232

Synthesis of (S)-5-(2-(2-(3,5-difluorophenyl)-1-(2-(3-(trifluoromethyl)-6,7-dihydrothiopyrano[4,3-c]pyrazol-1(4H)-yl)acetamido)ethyl)pyridin-3-yl)-2-fluorobenzamide (**232**):

Compound 232 was prepared according to the method presented for the synthesis of Example 122 substituting dihydro-2H-thiopyran-4(3H)-one for **122B** to provide 130 mg of title compound: ¹H NMR (400 MHz, cdcl₃) δ 8.53 (dd, 1H), 7.69 – 7.55 (m, 2H), 7.45 (dd, 1H), 7.30 – 7.07 (m, 3H), 6.88 (d, 1H), 6.72 (d, 1H), 6.51 (ddd, 1H), 6.13 (d, 2H), 5.41 (dd, 1H), 3.68 (d, 2H), 2.93 – 2.64 (m, 6H). MS (*m/z*) 620 [M+H]⁺.

Example 233



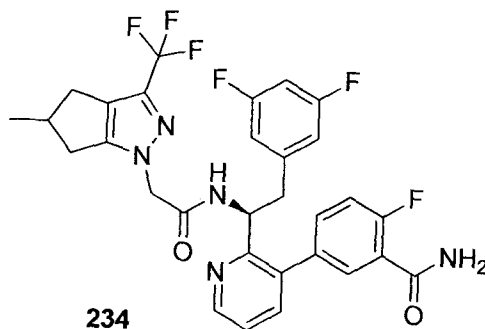
Synthesis of ethyl 2-(3-(difluoromethyl)-5-oxo-3b,4,4a,5-tetrahydro-1H-cyclopropa[3,4]cyclopenta[1,2-c]pyrazol-1-yl)acetate:

Compound 233A was prepared according to the method presented for the synthesis of Example 181 substituting **60A** for **122D** to provide 450 mg of title compound. MS (m/z) 271 [$M+H$]⁺.

Synthesis of 5-(2-((1S)-1-(2-(3-(difluoromethyl)-5-oxo-3b,4,4a,5-tetrahydro-1H-cyclopropa[3,4]cyclopenta[1,2-c]pyrazol-1-yl)acetamido)-2-(3,5-difluorophenyl)ethyl)pyridin-3-yl)-2-fluorobenzamide (**233B**):

Compound 233B was prepared according to the method presented for the synthesis of Example 154 substituting **233A** for **181A** to provide 38 mg of title compound: ¹H NMR (400 MHz, cd₃od) δ 8.70 (dd, 1H), 7.79 – 7.68 (m, 1H), 7.57 – 7.48 (m, 1H), 7.42 – 7.24 (m, 2H), 7.16 (dd, 1H), 6.81 – 6.52 (m, 2H), 6.25 (d, 2H), 5.30 (dd, 1H), 3.12 – 2.93 (m, 2H), 2.76 – 2.63 (m, 1H), 2.46 (dt, 1H), 1.65 – 1.48 (m, 2H). MS (m/z) 596 [$M+H$]⁺.

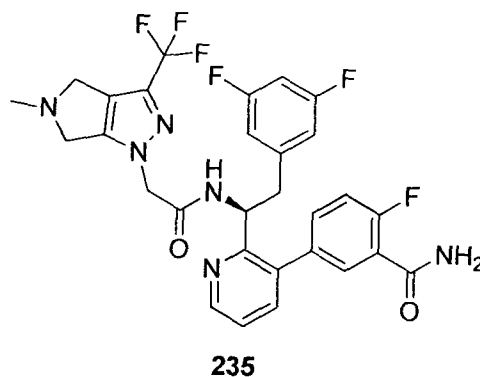
Example 234



Synthesis of 5-(2-((1S)-2-(3,5-difluorophenyl)-1-(2-(5-methyl-3-(trifluoromethyl)-5,6-dihydrocyclopenta[c]pyrazol-1(4H)-yl)acetamido)ethyl)pyridin-3-yl)-2-fluorobenzamide (**234**):

Compound **234** was prepared according to the method presented for the synthesis of Example 122 substituting 3-methylcyclopentanone for **122B** to provide 42 mg of title compound: ^1H NMR (400 MHz, cd_3od) δ 8.70 (d, 1H), 7.68 (dd, 1H), 7.47 (dd, 2H), 7.35 (s, 1H), 7.29 – 7.16 (m, 1H), 6.75 – 6.61 (m, 1H), 6.33 (d, 2H), 5.44 – 5.30 (m, 1H), 4.77 (s, 2H), 3.07 (t, 3H), 2.84 (dddd, 2H), 2.34 – 2.19 (m, 2H), 1.25 – 1.12 (m, 3H). MS (m/z) 602 $[\text{M}+\text{H}]^+$.

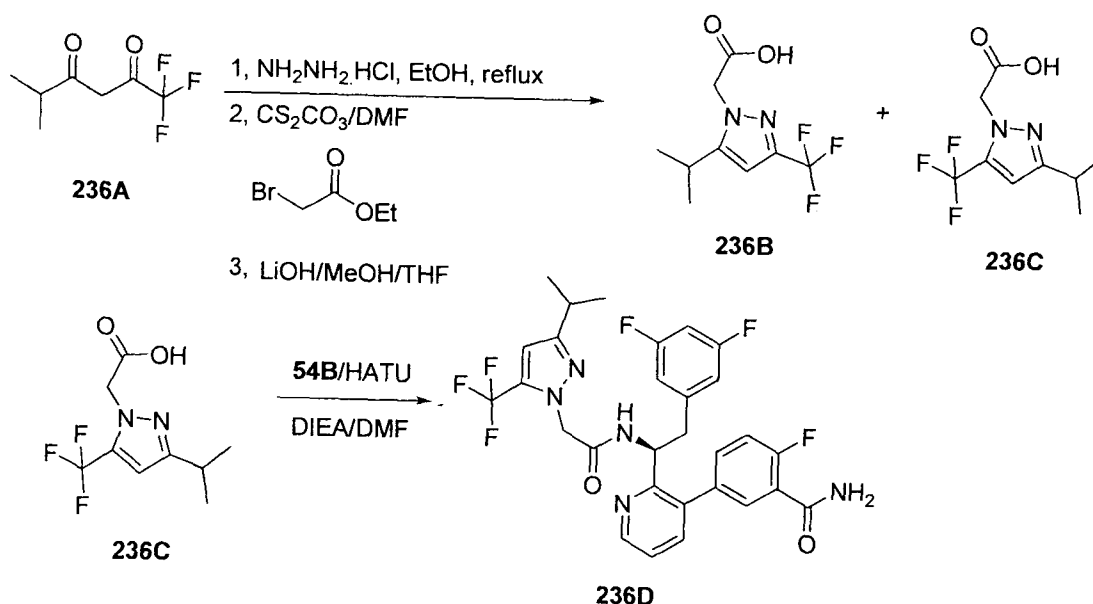
10 Example 235



Synthesis of (S)-5-(2-(2-(3,5-difluorophenyl)-1-(2-(5-methyl-3-(trifluoromethyl)-5,6-dihydropyrrolo[3,4-c]pyrazol-1(4H)-yl)acetamido)ethyl)pyridin-3-yl)-2-fluorobenzamide (**235**):

Compound **235** was prepared according to the method presented for the synthesis of Example 210 substituting **251** for **200B** to provide 22 mg of title compound: ^1H NMR (400 MHz, cd_3od) δ 8.71 (dd, 1H), 7.62 (ddd, 1.6 Hz, 1H), 7.53 (d, 1H), 7.43 (ddd, 1H), 7.23 (dd, 2H), 6.67 (dd, 1H), 6.33 (t, 2H), 5.38 – 5.27 (m, 1H), 4.95 (d, 2H), 4.53 – 4.39 (m, 2H), 4.30 – 4.14 (m, 2H), 3.16 – 3.04 (m, 2H), 3.01 (d, 3H). MS (m/z) 603 $[\text{M}+\text{H}]^+$.

Example 236



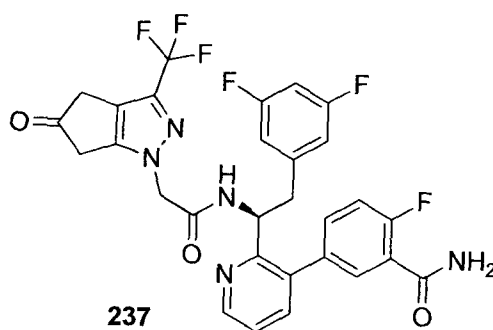
Synthesis of 2-(5-isopropyl-3-(trifluoromethyl)-1H-pyrazol-1-yl)acetic acid (**236B**) and 2-(3-isopropyl-5-(trifluoromethyl)-1H-pyrazol-1-yl)acetic acid (**236C**):

Compound 236B and 236C were prepared according to the method presented for the synthesis of Example 238 substituting 1,1,1-trifluoro-5-methylhexane-2,4-dione for 1,1,1-trifluoro-5,5-dimethylhexane-2,4-dione (**238A**) to provide 420 mg of **236B** and 400 mg of **236C**. **236B**: MS (*m/z*) 237 [M+H]⁺. **236C**: MS (*m/z*) 237 [M+H]⁺.

Synthesis of (S)-5-(2-(2-(3,5-difluorophenyl)-1-(2-(3-isopropyl-5-(trifluoromethyl)-1H-pyrazol-1-yl)acetamido)ethyl)pyridin-3-yl)-2-fluorobenzamide (**236D**):

Compound 236D was prepared according to the method presented for the synthesis of Example 54 utilizing **54B** and 2-(3-isopropyl-5-(trifluoromethyl)-1H-pyrazol-1-yl)acetic acid (**236C**) to provide 22 mg of title compound: ¹H NMR (400 MHz, cd₃od) δ 8.70 (dd, 1H), 7.67 (dd, 1H), 7.55 – 7.40 (m, 2H), 7.33 (s, 1H), 7.22 (dd, 1H), 6.75 – 6.61 (m, 1H), 6.49 – 6.27 (m, 3H), 5.36 (t, 1H), 4.90 (s, 2H), 3.06 (d, 2H), 2.83 (dt, 1H), 1.24 – 1.09 (m, 6H). MS (*m/z*) 590 [M+H]⁺.

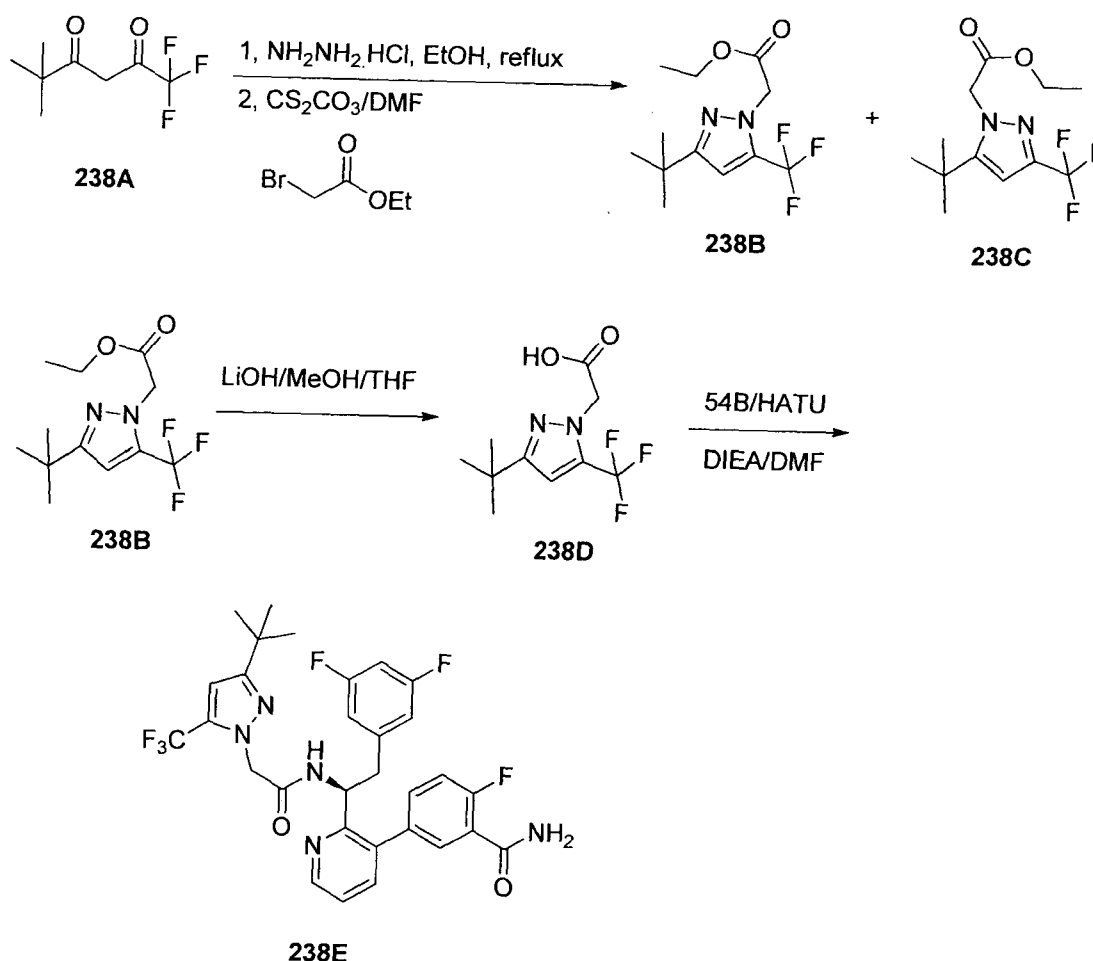
Example 237



Synthesis of (S)-5-(2-(2-(3,5-difluorophenyl)-1-(2-(5-oxo-3-(trifluoromethyl)-5,6-dihydrocyclopenta[c]pyrazol-1(4H)-yl)acetamido)ethyl)pyridin-3-yl)-2-fluorobenzamide (**237**):

Compound **237** was prepared according to the method presented for the synthesis of Example 122 substituting 3-ethoxycyclopent-2-enone for **122B** to provide 3 mg of title compound: ^1H NMR (400 MHz, cd_3od) δ 8.65 (dt, 1H), 7.54 (dd, 1H), 7.46 (dd, 1H), 7.42 – 7.26 (m, 2H), 7.19 (dd, 1H), 6.63 (t, 1H), 6.30 (d, 2H), 5.35 (t, 1H), 4.92 (s, 2H), 3.44 – 3.22 (m, 4H), 3.05 (qd, 2H). MS (m/z) 602 [$\text{M}+\text{H}$] $^+$.

10 Example 238



Synthesis of ethyl 2-(3-(tert-butyl)-5-(trifluoromethyl)-1H-pyrazol-1-yl)acetate (**238B**) and ethyl 2-(5-(tert-butyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl)acetate (**238C**):

15 A solution of 1,1,1-trifluoro-5,5-dimethylhexane-2,4-dione (1 g, 5.1 mmol) and hydrazine (280 mg, 5.6 mmol) in ethanol, was heated at reflux for 1 hour. Removed the solvent and used

without further purification. To a suspension of crude product and Cs_2CO_3 (1.6 g, 8.3 mmol) in DMF (6 mL) was added ethyl bromoacetate as a solution in DMF (5 mL). The reaction was stirred at room temperature for 5 hrs and then diluted with water. The mixture was extracted with EtOAc. The organics were dried over Na_2SO_4 , filtered and concentrated. The crude product was purified by SiO_2 chromatography eluting with a gradient of EtOAc in hexanes to provide 500 mg of **238B** and 750 mg of **238C**. **238B**:MS (m/z) 279 $[\text{M}+\text{H}]^+$. **238C**:MS (m/z) 279 $[\text{M}+\text{H}]^+$.

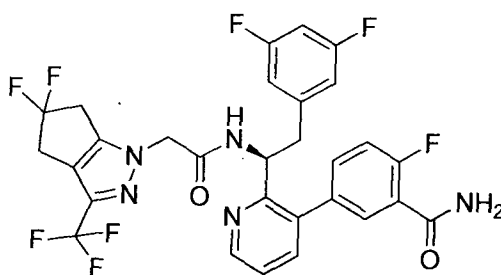
Synthesis of provide 2-(3-(tert-butyl)-5-(trifluoromethyl)-1H-pyrazol-1-yl)acetic acid (**238D**):

Compound **238D** was prepared according to the method presented for the synthesis of Example 74 substituting **238B** for **74B** to provide 460 mg of title compound. MS (m/z) 251 $[\text{M}+\text{H}]^+$.

Synthesis of (S)-5-(2-(1-(2-(3-(tert-butyl)-5-(trifluoromethyl)-1H-pyrazol-1-yl)acetamido)-2-(3,5-difluorophenyl)ethyl)pyridin-3-yl)-2-fluorobenzamide (**238E**):

Compound **238E** was prepared according to the method presented for the synthesis of Example 54 utilizing **54B** and 2-(3-(tert-butyl)-5-(trifluoromethyl)-1H-pyrazol-1-yl)acetic acid (**238D**) to provide 23 mg of title compound: ^1H NMR (400 MHz, cd_3od) δ 8.68 (dd, 1H), 7.64 (dd, 1H), 7.49 – 7.37 (m, 2H), 7.32 (s, 1H), 7.22 (dd, 1H), 6.67 (t, 1H), 6.40 (s, 1H), 6.32 (d, 2H), 5.35 (t, 1H), 5.03 (s, 2H), 3.03 (d, 2H), 1.27 (s, 9H). MS (m/z) 604 $[\text{M}+\text{H}]^+$.

Example 239



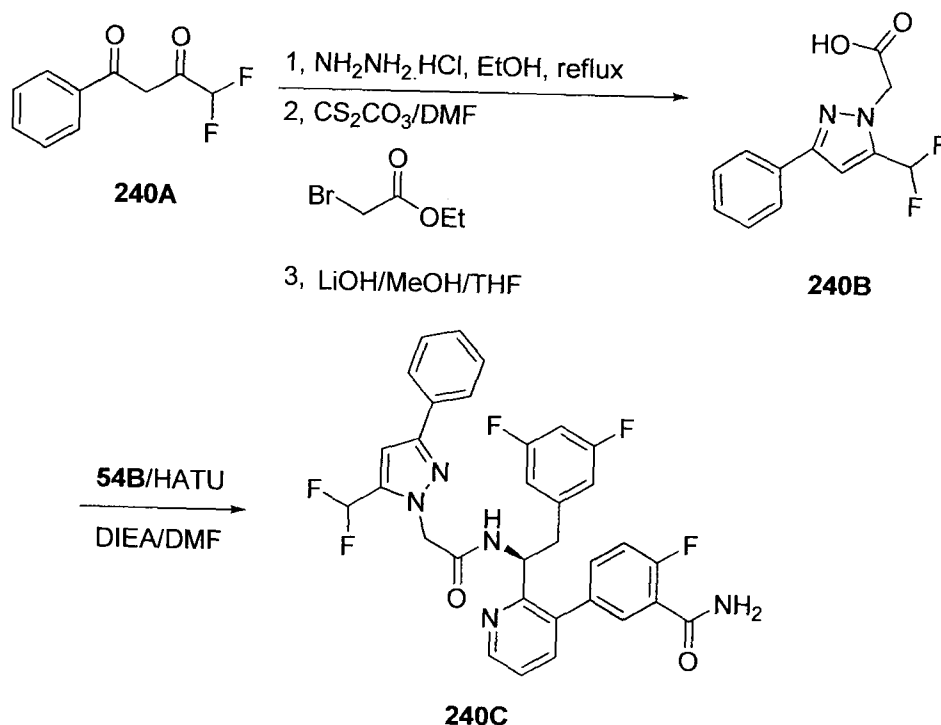
239

Synthesis of (S)-5-(2-(1-(2-(5,5-difluoro-3-(trifluoromethyl)-5,6-dihydrocyclopenta[c]pyrazol-1(4H)-yl)acetamido)-2-(3,5-difluorophenyl)ethyl)pyridin-3-yl)-2-fluorobenzamide (**239**):

Compound **239** was prepared according to the method presented for the synthesis of Example 150 utilizing **237** and 2-(5,5-difluoro-3-(trifluoromethyl)-5,6-dihydrocyclopenta[c]pyrazol-1(4H)-yl)acetic acid to provide 22 mg of title compound: ^1H NMR (400 MHz, cd_3od) δ 8.71 (dd,

1H), 7.66 (dd, 1H), 7.46 (dd, 2H), 7.34 (s, 1H), 7.22 (dd, 1H), 6.74 – 6.60 (m, 1H), 6.33 (d, 2H), 5.35 (t, 1H), 4.88 (s, 2H), 3.07 (d, 2H). MS (*m/z*) 624 [M+H]⁺.

Example 240



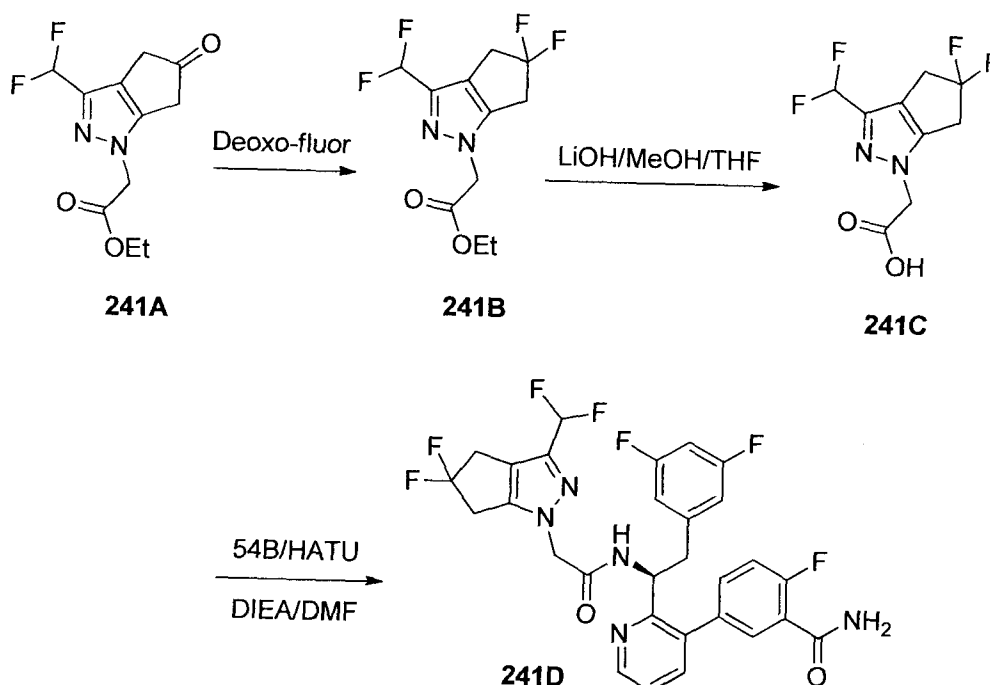
Synthesis of 22-(5-(difluoromethyl)-3-phenyl-1H-pyrazol-1-yl)acetic acid (**240B**):

Compound 240B was prepared according to the method presented for the synthesis of Example 238 substituting 4,4-difluoro-1-phenylbutane-1,3-dione for **238A** to provide 1.4 g of title compound. MS (*m/z*) 253 [M+H]⁺.

Synthesis of (S)-5-(2-(1-(2-(5-(difluoromethyl)-3-phenyl-1H-pyrazol-1-yl)acetamido)-2-(3,5-difluorophenyl)ethyl)pyridin-3-yl)-2-fluorobenzamide (**240C**):

Compound 240C was prepared according to the method presented for the synthesis of Example 54 utilizing **54B** and 2-(5-(difluoromethyl)-3-phenyl-1H-pyrazol-1-yl)acetic acid (**240B**) to provide 20 mg of title compound: ¹H NMR (400 MHz, cd₃od) δ 8.69 (dd, 1H), 7.63 (dd, 1H), 7.44 (dd, 1H), 7.41 – 7.34 (m, 5H), 7.22 (dd, 2H), 6.92 – 6.53 (m, 3H), 6.28 (d, 2H), 5.32 (t, 1H), 4.85 (s, 2H), 3.08 – 2.91 (m, 2H). MS (*m/z*) 606 [M+H]⁺.

Example 241



Synthesis of provide ethyl 2-(3-(difluoromethyl)-5-oxo-5,6-dihydrocyclopenta[c]pyrazol-1(4H)-yl)acetate (**241A**):

- Compound 241A was prepared according to the method presented for the synthesis of Example 122 substituting 3-ethoxycyclopent-2-enone for **122B** and ethyl 2,2-difluoroacetate for ethyl 2,2,2-trifluoroacetate to provide 1.6 g of title compound. MS (m/z) 259 $[M+H]^+$.

Synthesis of ethyl 2-(3-(difluoromethyl)-5,5-difluoro-5,6-dihydrocyclopenta[c]pyrazol-1(4H)-yl)acetate (**241B**):

- Compound 241B was prepared according to the method presented for the synthesis of Example 150 substituting **241A** for **446** to provide 250 mg of title compound. MS (m/z) 281 $[M+H]^+$.

Synthesis of 2-(3-(difluoromethyl)-5,5-difluoro-5,6-dihydrocyclopenta[c]pyrazol-1(4H)-yl)acetic acid (**241C**):

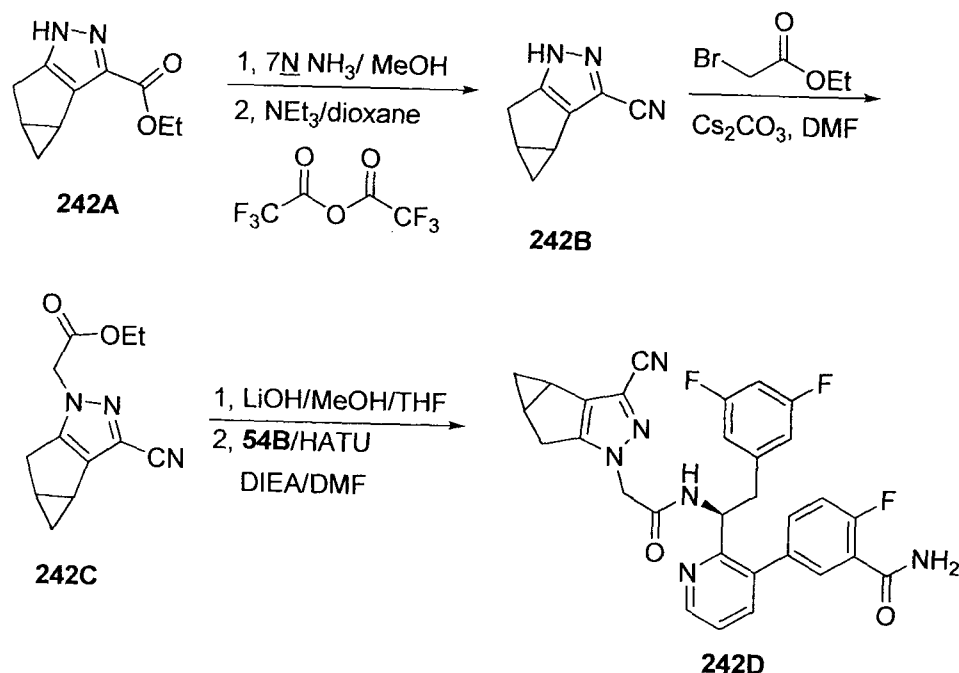
- Compound 241C was prepared according to the method presented for the synthesis of Example 74 substituting **241B** for **74B** to provide 238 mg of title compound. MS (m/z) 253 $[M+H]^+$.

Synthesis of (S)-5-(2-(1-(2-(3-(difluoromethyl)-5,5-difluoro-5,6-dihydrocyclopenta[c]pyrazol-1(4H)-yl)acetamido)-2-(3,5-difluorophenyl)ethyl)pyridin-3-yl)-2-fluorobenzamide (**241D**)

- Compound 241D was prepared according to the method presented for the synthesis of Example 54 utilizing **54B** and 2-(3-(difluoromethyl)-5,5-difluoro-5,6-dihydrocyclopenta[c]pyrazol-1(4H)-yl)acetic acid (**241C**) to provide 7 mg of title compound: ^1H NMR (400 MHz, cd_3od) δ 8.69 (d,

1H), 7.68 – 7.57 (m, 1H), 7.52 – 7.39 (m, 2H), 7.32 (s, 1H), 7.27 – 7.16 (m, 1H), 6.65 (dd, 2H), 6.33 (d, 2H), 5.34 (t, 1H), 3.22 (d, 2H), 3.05 (dd, 2H). MS (*m/z*) 606 [*M*+H]⁺.

Example 242



5

Synthesis of ethyl 3b,4,4a,5-tetrahydro-1H-cyclopropa[3,4]cyclopenta[1,2-c]pyrazole-3-carboxylate (**242A**):

Compound 242A was prepared according to the method presented for the synthesis of Example 90 substituting bicyclo[3.1.0]hexan-3-one (**122B**) for **90A** to provide 19.4 g of title compound.

10 MS (*m/z*) 193 [*M*+H]⁺.

Synthesis of 3b,4,4a,5-tetrahydro-1H-cyclopropa[3,4]cyclopenta[1,2-c]pyrazole-3-carbonitrile(**242B**):

A suspension of **242A** (1 g, 5.62 mmol) in 5 mL of NH₃ (7N in MeOH) was heated at 130 °C in
 15 sealed tube overnight. The reaction was monitored by LC/Mass until complete. Removed the solvent and used as crude. Dissolved the crude product in dioxane (5 mL) and added triethyl amine (4 mL). Trifluoromethanesulfonic anhydride (3.54 g, 16.8 mmol) was added to the mixture dropwise. The reaction was stirred for 2 hours. Diluted mixture with EtOAc (100 mL) and washed with aqueous NaHCO₃ twice. The layers were separated and the organic layer was
 20 washed 2x H₂O and 1x brine. The organics were dried over MgSO₄, filtered and concentrated. The crude product was purified by column chromatography on SiO₂ to provide 560 mg of title compound. MS (*m/z*) 146 [*M*+H]⁺.

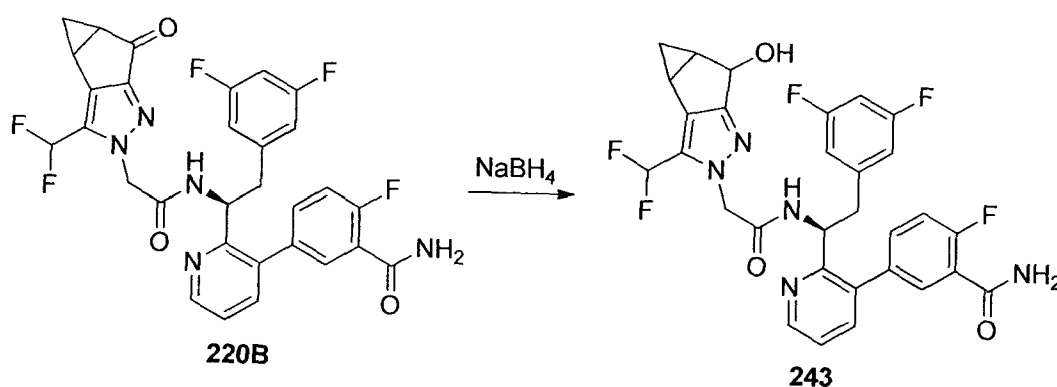
Synthesis of ethyl 2-(3-cyano-3b,4,4a,5-tetrahydro-1H-cyclopropa[3,4]cyclopenta[1,2-c]pyrazol-1-yl)acetate (**242C**):

Compound **242C** was prepared according to the method presented for the synthesis of Example 74 substituting 560mg of **242B** for **74A** to provide 463 mg of title compound. MS (m/z) 232 $[M+H]^+$.

Synthesis of 5-(2-((1S)-1-(2-(3-cyano-3b,4,4a,5-tetrahydro-1H-cyclopropa[3,4]cyclopenta[1,2-c]pyrazol-1-yl)acetamido)-2-(3,5-difluorophenyl)ethyl)pyridin-3-yl)-2-fluorobenzamide (**242D**):

Compound **242D** was prepared according to the method presented for the synthesis of Example 122 substituting **242C** for **122D** to provide 41 mg of title compound: ^1H NMR (400 MHz, cd_3od) δ 8.63 (dd, 1H), 7.57 (d, 1H), 7.48 – 7.33 (m, 2H), 7.25 (s, 1H), 7.15 (ddd, 1H), 6.68 – 6.53 (m, 1H), 6.25 (d, 2H), 5.26 (td, 1H), 4.75 – 4.56 (m, 2H), 2.98 (d, 2H), 2.83 – 2.69 (m, 1H), 2.61 (dd, 1H), 2.13 – 1.99 (m, 2H), 1.05 (dd, 1H), 0.26 – 0.14 (m, 1H). MS (m/z) 557 $[M+H]^+$.

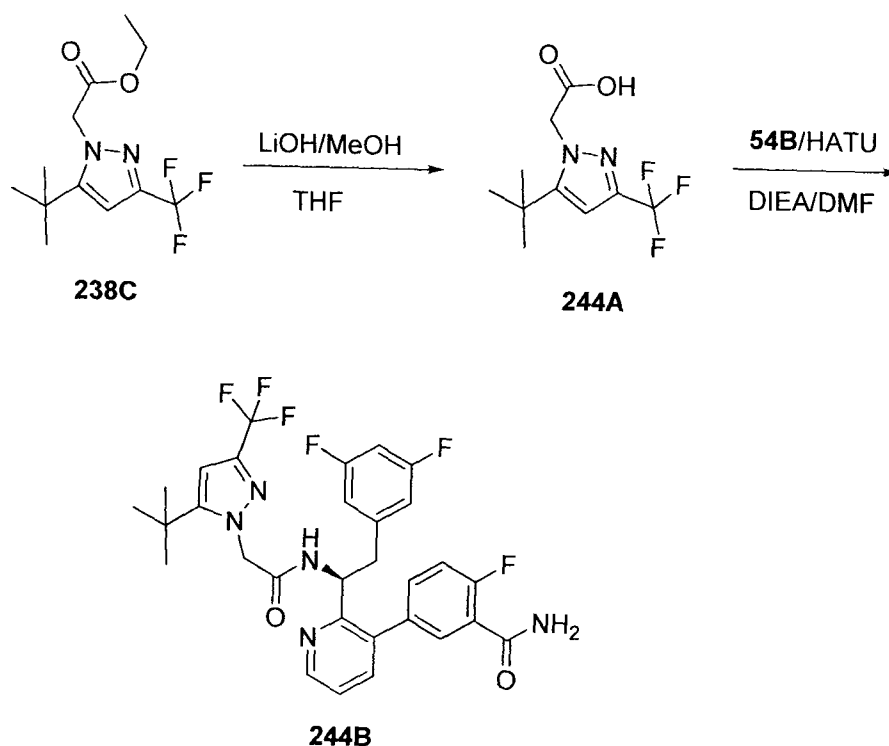
Example 243



Synthesis of 5-(2-((1S)-1-(2-(3-(difluoromethyl)-5-hydroxy-3b,4,4a,5-tetrahydro-2H-cyclopropa[3,4]cyclopenta[1,2-c]pyrazol-2-yl)acetamido)-2-(3,5-difluorophenyl)ethyl)pyridin-3-yl)-2-fluorobenzamide (**243**):

Compound **243** was prepared according to the method presented for the synthesis of Example 154 substituting **220B** for **154B** to provide 4 mg: ^1H NMR (400 MHz, cd_3od) δ 8.68 (d, 1H), 7.59 (dd, 1H), 7.48 – 7.32 (m, 2H), 7.32 – 7.13 (m, 2H), 6.87 (dd, 1H), 6.65 (t, 1H), 6.29 (d, 2H), 5.45 – 5.28 (m, 2H), 3.13 – 2.92 (m, 2H), 2.19 (d, 2H), 1.27 (s, 2H), 1.03 (dd, 1H), 0.83 (s, 1H). MS (m/z) 598 $[M+H]^+$.

Example 244



Synthesis of 2-(5-(tert-butyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl)acetic acid (**244A**):

Compound 244A was prepared according to the method presented for the synthesis of Example 74 substituting **238C** for **74B** to provide 450 mg of title compound. MS (m/z) 251 $[M+H]^+$.

5

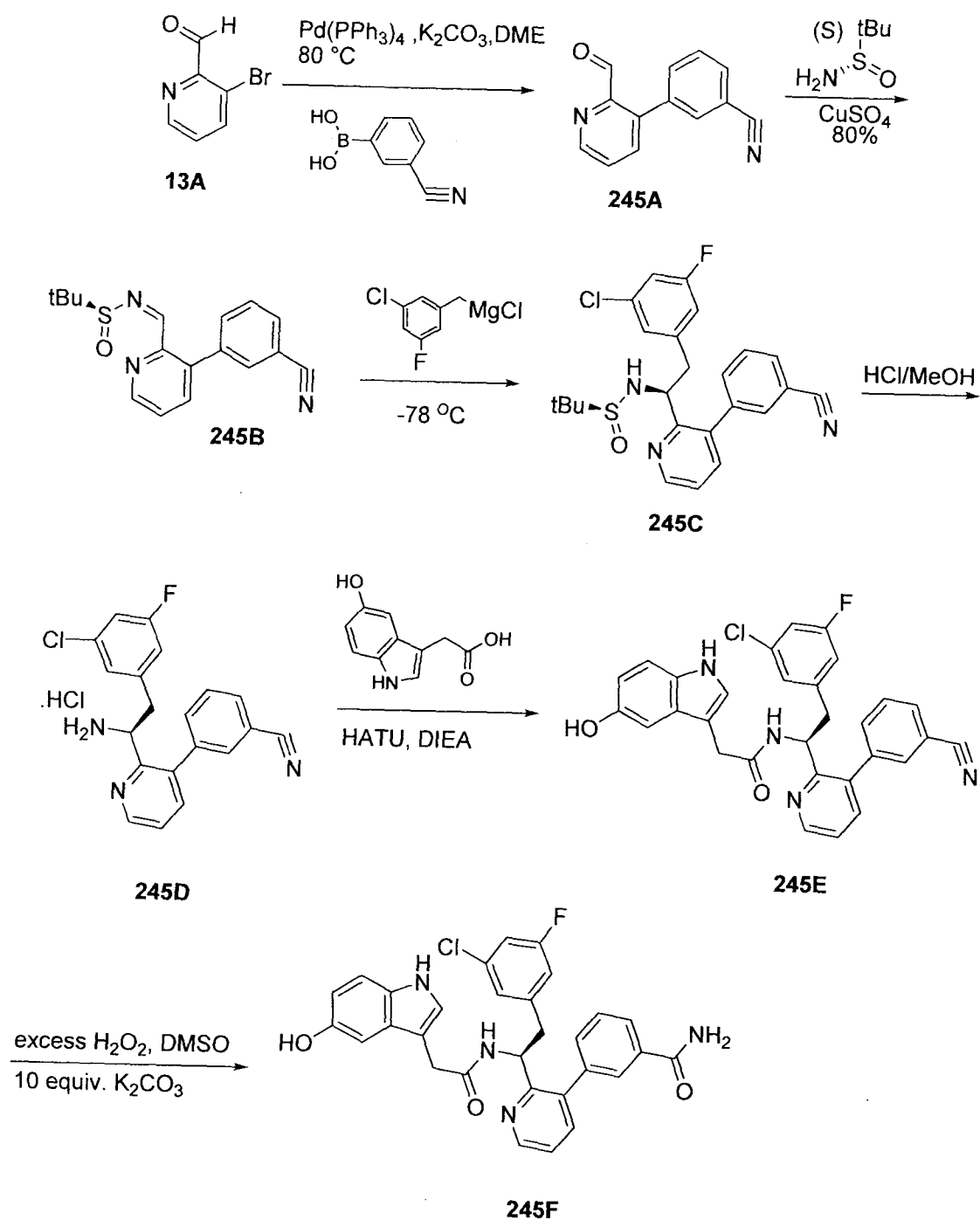
Synthesis of (S)-5-(2-(1-(2-(5-(tert-butyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl)acetamido)-2-(3,5-difluorophenyl)ethyl)pyridin-3-yl)-2-fluorobenzamide (**244B**):

Compound 244B was prepared according to the method presented for the synthesis of Example 54 utilizing **54B** and 2-(5-(tert-butyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl)acetic acid (**244A**) to provide 22 mg of title compound: ^1H NMR (400 MHz, cd_3od) δ 8.67 (dd, 1H), 7.65 (dd, 1H), 7.45 (dd, 1H), 7.39 (d, 1H), 7.31 (s, 1H), 7.23 (dd, 1H), 6.71 – 6.59 (m, 2H), 6.28 (d, 2H), 5.37 (t, 1H), 4.91 (d, 2H), 3.00 (d, 2H), 1.29 (s, 9H). MS (m/z) 604 $[M+H]^+$.

10

Example 245F

15



Synthesis of 3-(2-formylpyridin-3-yl)benzonitrile (**245A**):

Compound **245A** was prepared according to the method presented for the synthesis of Example 5 13 utilizing **13A** and (3-cyanophenyl)boronic acid to provide 3.8 g of title compound: MS (m/z) 209 $[\text{M}+\text{H}]^+$.

Synthesis of (S,Z)-N-((3-(3-cyanophenyl)pyridin-2-yl)methylene)-2-methylpropane-2-sulfonamide (**245B**):

Compound 245B was prepared according to the method presented for the synthesis of Example 13 substituting **245A** for **13B** to provide 4 g of title compound: MS (m/z) 312 $[M+H]^+$.

- 5 Synthesis of (S)-N-((S)-2-(3-chloro-5-fluorophenyl)-1-(3-(3-cyanophenyl)pyridin-2-yl)ethyl)-2-methylpropane-2-sulfonamide (**245C**):

Compound 245C was prepared according to the method presented for the synthesis of Example 13 substituting **245B** for **13C** and (3-chloro-5-fluorobenzyl)magnesium chloride to provide 1.9 g of title compound: MS (m/z) 456 $[M+H]^+$.

- 10 Synthesis of (S)-3-(2-(1-amino-2-(3-chloro-5-fluorophenyl)ethyl)pyridin-3-yl)benzonitrile hydrochloride (**245D**):

Compound 245D was prepared according to the method presented for the synthesis of Example 13 substituting **245C** for **13E** to provide 70 mg of title compound: MS (m/z) 352 $[M+H]^+$.

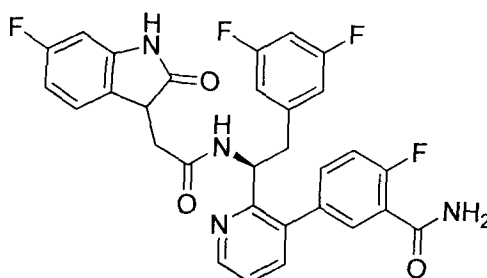
- 15 Synthesis of (S)-N-(2-(3-chloro-5-fluorophenyl)-1-(3-(3-cyanophenyl)pyridin-2-yl)ethyl)-2-(5-hydroxy-1H-indol-3-yl)acetamide (**245E**):

Compound 245E was prepared according to the method presented for the synthesis of Example 13 substituting **245D** for **13F** to provide 120 mg of title compound: MS (m/z) 525 $[M+H]^+$.

- 20 Synthesis of (S)-3-(2-(2-(3-chloro-5-fluorophenyl)-1-(2-(5-hydroxy-1H-indol-3-yl)acetamido)ethyl)pyridin-3-yl)benzamide (**245F**):

H₂O₂ (30 wt %, excess) was added to a suspension of **245E** (120 mg, 0.19 mmol) and potassium carbonate (210 mg, 1.52 mmol) in DMSO (1 mL) at 0 °C. The suspension and stirred for 1 hour, filtered and the filtrate was purified by RP HPLC using a C18 column with a gradient of H₂O, 0.1% TFA-acetonitrile, to provide 80 mg of the title product. ¹H NMR (400 MHz, dmso) δ 10.42 (s, 1H), 8.61 (dd, 1H), 8.44 (d, 1H), 7.91 (s, 1H), 7.83 (d, 1H), 7.66 (s, 1H), 7.56 (dd, 1H), 7.47 – 7.25 (m, 4H), 7.02 (d, 2H), 6.88 (s, 1H), 6.73 (d, 1H), 6.55 (s, 1H), 6.54 – 6.43 (m, 2H), 5.16 (dd, 2H), 3.36 (s, 2H), 2.88 (d, 2H). MS (m/z) 543 $[M+H]^+$.

- 30 Example 246

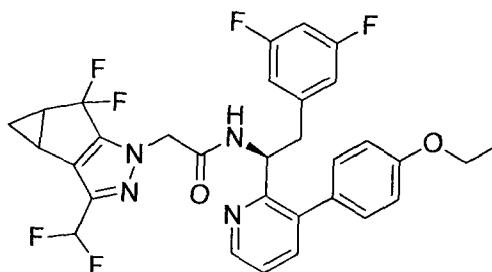
**246**

Synthesis of 5-(2-((1S)-2-(3,5-difluorophenyl)-1-(2-(6-fluoro-2-oxoindolin-3-yl)acetamido)ethyl)pyridin-3-yl)-2-fluorobenzamide (**246**):

- 5 Compound **246** was prepared according to the method presented for the synthesis of Example 54 utilizing **54B** and 2-(6-fluoro-2-oxoindolin-3-yl)acetic acid to provide 13 mg of title compound: ^1H NMR (400 MHz, cd_3od) δ 8.62 (d, 1H), 7.64 – 7.53 (m, 1H), 7.43 – 7.33 (m, 1H), 7.31 – 7.00 (m, 3H), 6.95 – 6.79 (m, 1H), 6.68 – 6.35 (m, 3H), 6.30 – 6.12 (m, 2H), 5.24 (dd, 1H), 3.62 (s, 1H), 3.01 – 2.72 (m, 3H), 2.65 – 2.49 (m, 1H). MS (m/z) 563 $[\text{M}+\text{H}]^+$.

10

Example 247

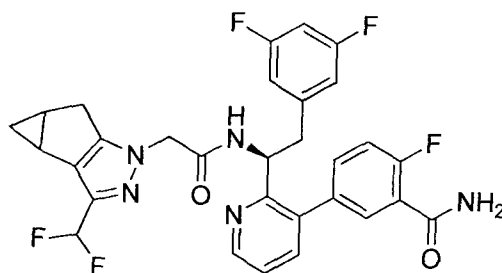
**247**

Synthesis of 2-(3-(difluoromethyl)-5,5-difluoro-3b,4,4a,5-tetrahydro-1H-cyclopropa[3,4]cyclopenta[1,2-c]pyrazol-1-yl)-N-((S)-2-(3,5-difluorophenyl)-1-(3-(4-ethoxyphenyl)pyridin-2-yl)ethyl)acetamide (**247**):

- 15 Compound **247** was prepared according to the method presented for the synthesis of Example 68 utilizing **68A** and (4-ethoxyphenyl)boronic acid to provide 8 mg of title compound: ^1H NMR (400 MHz, cd_3od) δ 8.61 (d, 1H), 7.61 (d, 1H), 7.40 (dd, 4.9 Hz, 1H), 7.03 – 6.94 (m, 2H), 6.90 (dd, 2H), 6.86 – 6.51 (m, 3H), 6.25 (d, 2H), 5.48 (d, 1H), 4.05 (q, 2H), 2.96 (t, 2H), 2.46 (s, 2H), 1.39 (t, 4H), 1.07 (s, 1H). MS (m/z) 601 $[\text{M}+\text{H}]^+$.

20

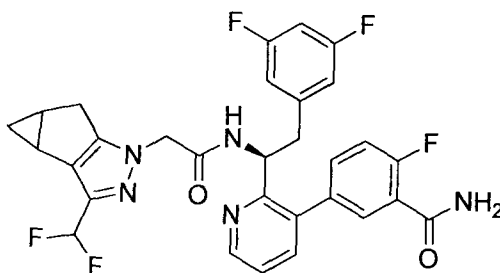
Example 248

**248**

Synthesis of 5-(2-((1S)-1-(2-(3-(difluoromethyl)-3b,4,4a,5-tetrahydro-1H-cyclopropa[3,4]cyclopenta[1,2-c]pyrazol-1-yl)acetamido)-2-(3,5-difluorophenyl)ethyl)pyridin-3-yl)-2-fluorobenzamide (**248**):

- 5 **248** was separated from the diastereomeric mixture of **198** by semi-preparative chiral HPLC fitted with a Chiralcel AZ-H column running a 70:30 mixture of Hep:IPA. The fast eluent was collected to obtain 3 mg of the single diastereomer: ¹H NMR (400 MHz, cd₃od) δ 8.50 (dd, 1H), 7.46 (dd, 1H), 7.34 – 7.10 (m, 3H), 7.04 (dd, 8.5 Hz, 1H), 6.58 – 6.23 (m, 2H), 6.11 (t, 2H), 5.15 (t, 1H), 4.57 – 4.38 (m, 2H), 2.93 – 2.79 (m, 2H), 2.59 (dd, 1H), 2.43 (d, 1H), 1.99 – 1.77 (m, 10 2H), 0.86 (td, 1H), 0.01 (dd, 1H). MS (*m/z*) 582 [M+H]⁺.

Example 249

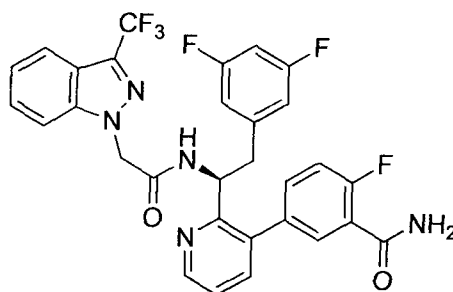
**249**

Synthesis of 5-(2-((1S)-1-(2-(3-(difluoromethyl)-3b,4,4a,5-tetrahydro-1H-cyclopropa[3,4]cyclopenta[1,2-c]pyrazol-1-yl)acetamido)-2-(3,5-difluorophenyl)ethyl)pyridin-3-yl)-2-fluorobenzamide (**249**):

- 249** was separated from the diastereomeric mixture of **198** by semi-preparative chiral HPLC fitted with a Chiralcel AZ-H column running a 70:30 mixture of Hep:IPA. The slow eluent was collected to obtain 3 mg of the single diastereomer: ¹H NMR (400 MHz, cd₃od) δ 8.47 (dd, 1H), 7.40 (dd, 1H), 7.21 (dd, 2H), 7.10 (s, 1H), 7.01 (dd, 1H), 6.54 – 6.20 (m, 2H), 6.11 (d, 2H), 20

5.12 (t, 1H), 4.54 – 4.37 (m, 2H), 2.93 – 2.72 (m, 2H), 2.58 (dd, 1H), 2.44 (d, 1H), 1.86 (dd, 2H), 0.85 (td, 1H), 0.02 (dd, 1H). MS (m/z) 582 $[M+H]^+$.

Example 250

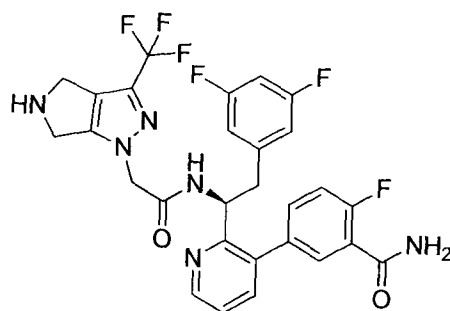


250

Synthesis of (S)-5-(2-(2-(3,5-difluorophenyl)-1-(2-(3-(trifluoromethyl)-1H-indazol-1-yl)acetamido)ethyl)pyridin-3-yl)-2-fluorobenzamide (**250**):

Compound 250 was prepared according to the method presented for the synthesis of Example 54 utilizing **54B** and 2-(3-(trifluoromethyl)-1H-indazol-1-yl)acetic acid to provide 36 mg of title compound: ^1H NMR (400 MHz, dmso) δ 9.13 (d, 1H), 8.71 (dd, 1H), 7.73 (d, 1H), 7.67 – 7.55 (m, 3H), 7.52 – 7.35 (m, 4H), 7.28 (ddd, 2H), 6.92 (t, 1H), 6.57 (d, 2H), 5.27 – 5.09 (m, 3H), 3.03 (d, 2H). MS (m/z) 598 $[M+H]^+$.

Example 251



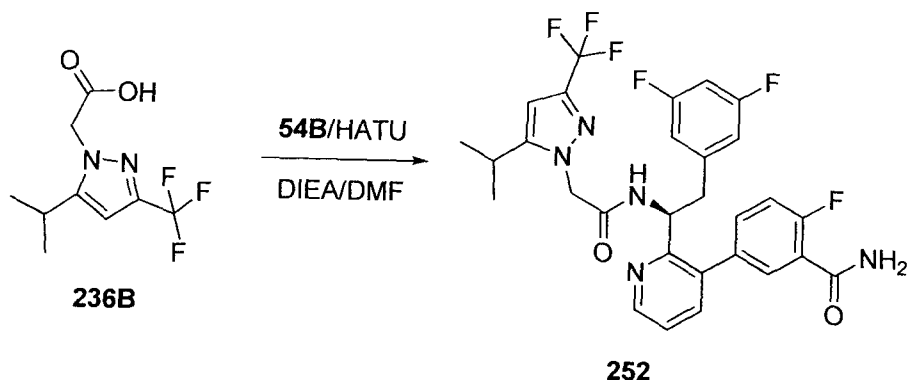
251

Synthesis of (S)-5-(2-(2-(3,5-difluorophenyl)-1-(2-(3-(trifluoromethyl)-5,6-dihydropyrrolo[3,4-c]pyrazol-1(4H)-yl)acetamido)ethyl)pyridin-3-yl)-2-fluorobenzamide (**251**):

Compound 251 was prepared according to the method presented for the synthesis of Example 200 substituting **227** for **200A** to provide 7 mg of title compound: ^1H NMR (400 MHz, cd_3od) δ

8.70 (dd, 1H), 7.58 (dd, 2H), 7.40 (dd, 1H), 7.19 (t, 2H), 6.66 (tt, 1H), 6.33 (t, 2H), 5.32 (dd, 1H), 4.96 (s, 2H), 4.51 (s, 2H), 4.46 (s, 2H), 3.08 (qd, 2H). MS (m/z) 589 $[M+H]^+$.

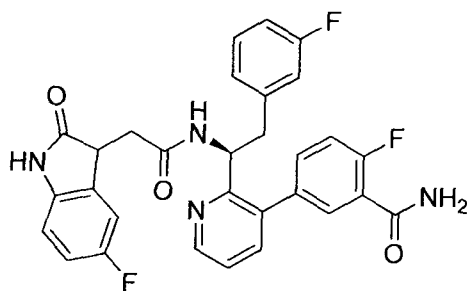
Example 252



Synthesis of (S)-5-(2-(2-(3,5-difluorophenyl)-1-(2-(5-isopropyl-3-(trifluoromethyl)-1H-pyrazol-1-yl)acetamido)ethyl)pyridin-3-yl)-2-fluorobenzamide (**252**):

Compound 252 was prepared according to the method presented for the synthesis of Example 54 utilizing **54B** and 2-(5-isopropyl-3-(trifluoromethyl)-1H-pyrazol-1-yl)acetic acid (**236B**) to provide 18 mg of title compound: ^1H NMR (400 MHz, cd_3od) δ 8.70 (dd, 1H), 7.65 (dd, 1H), 7.45 (dd, 2H), 7.33 (s, 1H), 7.22 (dd, 1H), 6.67 (t, 1H), 6.40 (s, 1H), 6.34 (d, 2H), 5.36 (t, 1H), 4.90 (s, 2H), 3.06 (d, 2H), 2.83 (dt, 1H), 1.17 (t, 6H). MS (m/z) 590 $[M+H]^+$.

Example 253



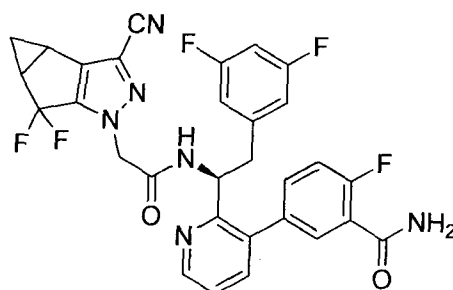
253

Synthesis of 2-fluoro-5-(2-(((1S)-1-(2-(5-fluoro-2-oxoindolin-3-yl)acetamido)-2-(3-fluorophenyl)ethyl)pyridin-3-yl)benzamide (**253**):

Compound 253 was prepared according to the method presented for the synthesis of Example 59 utilizing **59D** and 2-(5-fluoro-2-oxoindolin-3-yl)acetic acid to provide 21 mg of title compound: ^1H NMR (400 MHz, cd_3od) δ 8.62 (ddd, 1H), 7.56 (ddd, 1H), 7.45 – 7.24 (m, 2H), 7.22 – 6.80

(m, 5H), 6.73 (ddd, 2H), 6.43 (t, 1H), 6.40 – 6.32 (m, 1H), 5.23 (dt, 1H), 3.89 – 3.74 (m, 1H), 3.03 – 2.88 (m, 2H), 2.66 – 2.54 (m, 2H). MS (m/z) 545 $[M+H]^+$.

Example 254



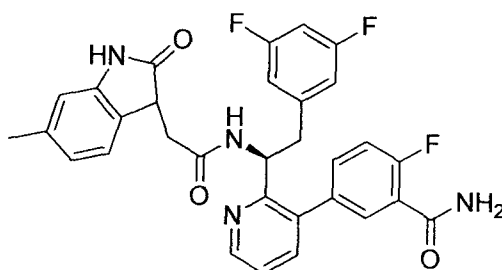
254

Synthesis of 5-(2-((1S)-1-(2-(3-cyano-5,5-difluoro-3b,4,4a,5-tetrahydro-1H-cyclopropa[3,4]cyclopenta[1,2-c]pyrazol-1-yl)acetamido)-2-(3,5-difluorophenyl)ethyl)pyridin-3-yl)-2-fluorobenzamide (**254**):

Compound 254 was prepared according to the method presented for the synthesis of Example

181 substituting **242C** for **122D** to provide 28 mg of title compound: ^1H NMR (400 MHz, cd_3od) δ 8.72 (dd, 1H), 7.67 (d, 1H), 7.48 (dd, 1H), 7.34 (d, 2H), 7.27 – 7.16 (m, 1H), 6.67 (t, 1H), 6.31 (d, 2H), 5.34 (t, 1H), 4.90 (s, 2H), 3.06 (dd, 2H), 2.52 (d, 2H), 1.42 (dd, 1H), 1.11 (s, 1H). MS (m/z) 593 $[M+H]^+$.

15 Example 255



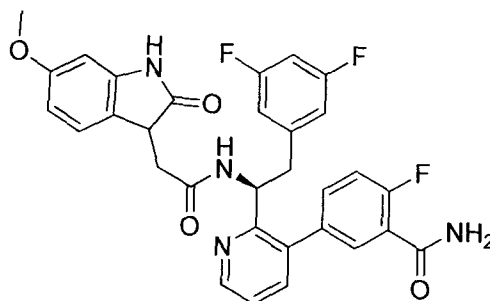
255

Synthesis of 5-(2-((1S)-2-(3,5-difluorophenyl)-1-(2-(6-methyl-2-oxoindolin-3-yl)acetamido)ethyl)pyridin-3-yl)-2-fluorobenzamide (**255**):

Compound 225 was prepared according to the method presented for the synthesis of Example 54

utilizing **54B** and 2-(6-methyl-2-oxoindolin-3-yl)acetic acid to provide 7 mg of title compound: ^1H NMR (400 MHz, cd_3od) δ 8.71 (t, 1H), 7.75 – 7.66 (m, 1H), 7.50 (td, 1H), 7.46 – 7.09 (m, 3H), 7.08 – 6.52 (m, 5H), 6.29 (t, 2H), 5.32 (dd, 1H), 3.66 (d, 1H), 3.06 – 2.93 (m, 2H), 2.93 – 2.56 (m, 3H), 2.23 (d, 3H). MS (m/z) 559 $[M+H]^+$.

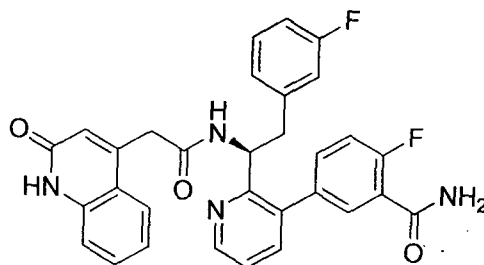
Example 256

**256**

- 5 Synthesis of 5-(2-((1S)-2-(3,5-difluorophenyl)-1-(2-(6-methoxy-2-oxoindolin-3-yl)acetamido)ethyl)pyridin-3-yl)-2-fluorobenzamide (**256**):

Compound 256 was prepared according to the method presented for the synthesis of Example 54 utilizing **54B** and 2-(6-methoxy-2-oxoindolin-3-yl)acetic acid to provide 19 mg of title compound: ^1H NMR (400 MHz, cd_3od) δ 8.68 (dd, 1H), 7.61 (dd, 1H), 7.53 – 7.34 (m, 2H), 7.34 – 7.08 (m, 2H), 7.03 (d, 1H), 6.74 – 6.57 (m, 1H), 6.56 – 6.22 (m, 4H), 5.31 (dt, 1H), 3.91 – 3.70 (m, 4H), 3.13 – 2.89 (m, 2H), 2.76 – 2.58 (m, 2H). MS (m/z) 575 $[\text{M}+\text{H}]^+$.

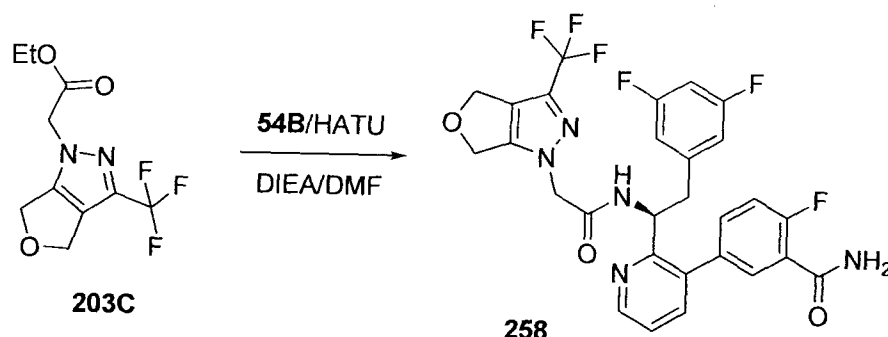
Example 257

**257**

- 15 Synthesis of (S)-2-fluoro-5-(2-(2-(3-fluorophenyl)-1-(2-(2-oxo-1,2-dihydroquinolin-4-yl)acetamido)ethyl)pyridin-3-yl)benzamide (**257**):

Compound 257 was prepared according to the method presented for the synthesis of Example 59 utilizing **59D** and 2-(2-oxo-1,2-dihydroquinolin-4-yl)acetic acid to provide 15 mg of title compound: ^1H NMR (400 MHz, cd_3od) δ 8.73 (dd, 1H), 7.67 (dd, 2H), 7.56 – 7.45 (m, 2H), 7.40 – 7.24 (m, 3H), 7.23 – 7.10 (m, 2H), 7.04 (dd, 1H), 6.81 (dd, 1H), 6.60 – 6.41 (m, 3H), 5.33 (t, 1H), 3.85 (s, 2H), 3.13 – 3.02 (m, 2H). MS (m/z) 539 $[\text{M}+\text{H}]^+$.

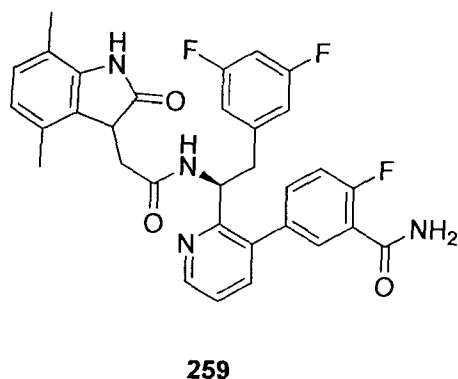
Example 258



Synthesis of (S)-5-(2-(2-(3,5-difluorophenyl)-1-(2-(3-(trifluoromethyl)-4,6-dihydro-1H-furo[3,4-c]pyrazol-1-yl)acetamido)ethyl)pyridin-3-yl)-2-fluorobenzamide (**258**):

Compound **258** was prepared according to the method presented for the synthesis of Example 122 substituting **203C** for **122D** to provide 42 mg of title compound: ^1H NMR (400 MHz, cd_3od) δ 8.70 (dd, 1H), 7.63 (dd, 1H), 7.54 – 7.39 (m, 2H), 7.31 (s, 1H), 7.22 (dd, 1H), 6.66 (t, 1H), 6.32 (d, 2H), 5.34 (t, 1H), 4.90 – 4.84 (m, 4H), 4.78 (d, 2H), 3.16 – 2.97 (m, 2H). MS (m/z) 590 $[\text{M}+\text{H}]^+$.

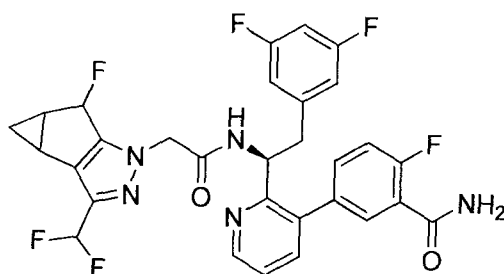
Example 259



Synthesis of 5-(2-((1S)-2-(3,5-difluorophenyl)-1-(2-(4,7-dimethyl-2-oxoindolin-3-yl)acetamido)ethyl)pyridin-3-yl)-2-fluorobenzamide (**259**):

Compound **259** was prepared according to the method presented for the synthesis of Example 54 utilizing **54B** and 2-(4,7-dimethylindolin-3-yl)acetic acid to provide 21 mg of title compound: ^1H NMR (400 MHz, cd_3od) δ 8.76 – 8.65 (m, 1H), 7.62 (dd, 1H), 7.46 (dd, 1H), 7.12 (ddd, 3H), 6.93 – 6.57 (m, 4H), 6.29 (dd, 3H), 5.30 – 5.15 (m, 1H), 3.69 (d, 1H), 3.14 – 2.82 (m, 5H), 2.15 (d, 6H). MS (m/z) 573 $[\text{M}+\text{H}]^+$.

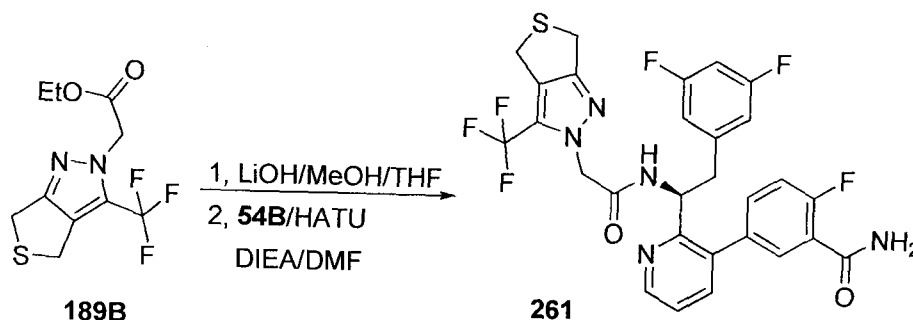
Example 260

**260**

Synthesis of 5-(2-((1S)-1-(2-(3-(difluoromethyl)-5-fluoro-3b,4,4a,5-tetrahydro-1H-cyclopropa[3,4]cyclopenta[1,2-c]pyrazol-1-yl)acetamido)-2-(3,5-difluorophenyl)ethyl)pyridin-3-yl)-2-fluorobenzamide (**260**):

Compound 260 was prepared according to the method presented for the synthesis of Example 390 substituting **212** for **334** to provide 18 mg of title compound: ^1H NMR (400 MHz, cd_3od) δ 8.73 – 8.55 (m, 1H), 7.67 – 7.53 (m, 1H), 7.50 – 7.08 (m, 4H), 6.78 – 6.37 (m, 2H), 6.22 (td, 2H), 6.14 – 5.86 (m, 1H), 5.46 (dd, 1H), 5.25 (ddd, 1H), 3.03 – 2.85 (m, 2H), 2.36 – 2.10 (m, 2H), 1.21 (dd, 1H), 1.12 – 0.84 (m, 1H), 0.39 – 0.15 (m, 1H). MS (m/z) 600 $[\text{M}+\text{H}]^+$.

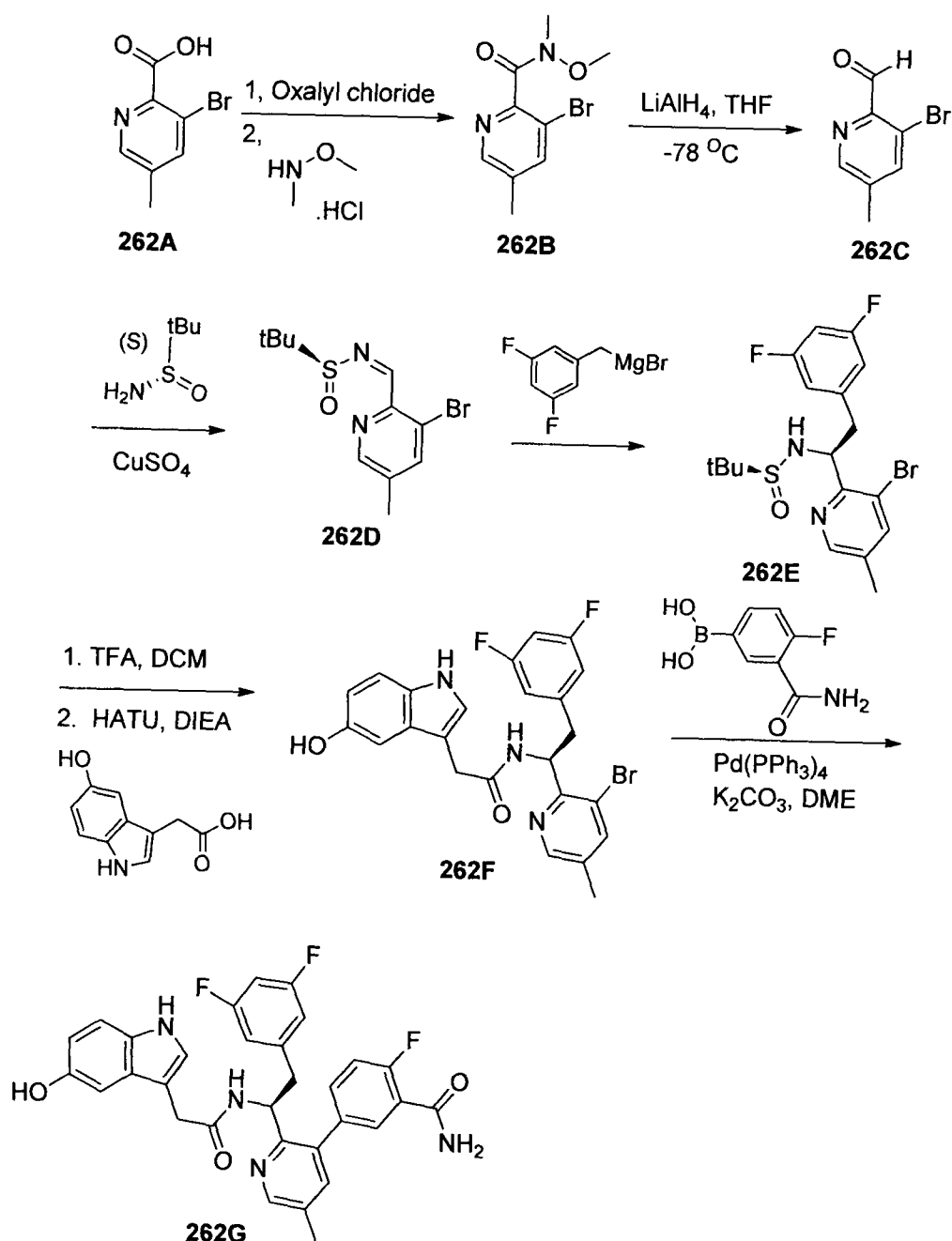
Example 261



Synthesis of (S)-5-(2-(2-(3,5-difluorophenyl)-1-(2-(3-(trifluoromethyl)-4,6-dihydro-2H-thieno[3,4-c]pyrazol-2-yl)acetamido)ethyl)pyridin-3-yl)-2-fluorobenzamide (**261**):

Compound 261 was prepared according to the method presented for the synthesis of Example 122 substituting **189B** for **122D** to provide to provide 31 mg of title compound: ^1H NMR (400 MHz, cd_3od) δ 8.73 – 8.59 (m, 1H), 7.53 (dd, 1H), 7.49 – 7.26 (m, 3H), 7.26 – 7.15 (m, 1H), 6.63 (t, 1H), 6.37 – 6.23 (m, 2H), 5.35 (t, 1H), 4.88 (d, 1H), 4.00 – 3.78 (m, 4H), 3.15 – 2.89 (m, 2H). MS (m/z) 606 $[\text{M}+\text{H}]^+$.

Example 262



Synthesis of 3-bromo-N-methoxy-N,5-dimethylpicolinamide (**262B**):

A solution of **262A** (1 g, 4.63 mmol) in oxalyl chloride (5 mL) was heated at 60 °C for 30 minutes. Removed the solvent and dissolved in DCM (10 mL). Cooled mixture to 0 °C. N,O-Dimethylhydroxylamine hydrochloride (0.57 g, 5.84 mmol) and DIEA (1.61 mL, 9.26 mmol) were added to the mixture slowly. After 1 hour, diluted the reaction with EtOAc (50 mL) and washed with brine (20 mL) twice. The organic layer was dried with Na₂SO₄, concentrated and purified by flash column (R_f: 0.3 EtOAc/Hexanes = 40%) to provide 1.07 g of title compound.

MS (*m/z*) 259 [M+H]⁺.

Synthesis of 3-bromo-5-methylpicolinaldehyde (**262C**):

A solution of **262B** (1.7 g, 3.7 mmol) in tetrahydrofuran (20 mL) at -78 °C, LiAlH₄ (5.55 mL, 1M in THF) was added to a solution dropwise. The mixture was stirred for 3 hours at -78 °C.

5 Acidified by 1N hydrochloride in methanol at -78 °C and warmed up to r.t.. The mixture was extracted with EtOAc (50 mL) twice. The organic layer was dried with Na₂SO₄, concentrated and purified by flash column (Rf: 0.3 EtOAc/Hexanes = 5%) to provide 0.83 g of title compound. MS (*m/z*) 200 [M+H]⁺.

10 Synthesis of (S)-N-(1-(3-bromo-5-methylpyridin-2-yl)-2-(3,5-difluorophenyl)ethyl)-2-(5-hydroxy-1H-indol-3-yl)acetamide (**262F**):

Compound **262F** was prepared according to the method presented for the synthesis of Example 38 substituting **262C** (0.83, 3.7 mmol) for **38A** to provide 360 mg of title compound: MS (*m/z*) 500 [M+H]⁺.

15

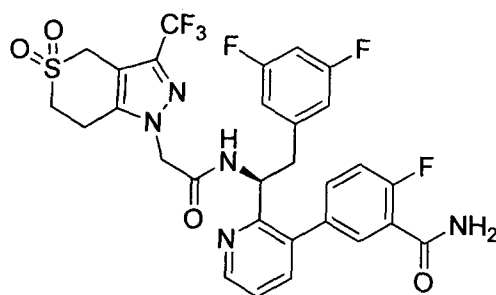
Synthesis of (S)-5-(2-(2-(3,5-difluorophenyl)-1-(2-(5-hydroxy-1H-indol-3-yl)acetamido)ethyl)-5-methylpyridin-3-yl)-2-fluorobenzamide(**262G**):

262F (48.7 mg, 0.1 mmol), potassium carbonate (27 mg, 0.2 mmol) in 0.5 ml of water,

tetrakis(triphenylphosphine) palladium(0) (8 mg, 0.007 mmol) and 3-cyanophenylboronic acid

20 (0.12 mmol) in DME (1.5 mL) was heated to 120 °C for 30 minutes under microwave irradiation. Solvents were concentrated *in vacuo* and the residue was purified by RP HPLC using a C18 column with a gradient of 0.1% TFA-acetonitrile in 0.1%TFA/ H₂O to provide 7.5 mg of title compound: ¹H NMR (400 MHz, cd₃od) δ 8.38 (s, 1H), 7.56 (s, 1H), 7.43 (s, 1H), 7.33 – 7.11 (m, 3H), 7.06 (s, 1H), 6.72 (d, 1H), 6.66 (d, 2H), 6.26 (d, 2H), 5.47 (s, 2H), 5.36 – 5.22 (m, 25 1H), 3.59 (d, 2H), 3.05 – 2.85 (m, 2H), 2.38 (s, 3H); MS (*m/z*) 559 [M+H]⁺

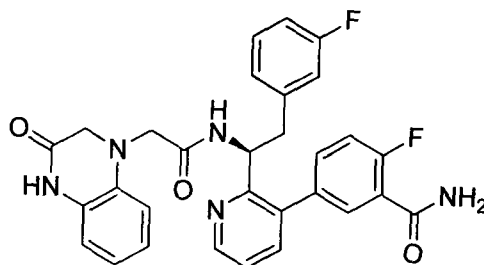
Example 263

**263**

Synthesis of (S)-5-(2-(2-(3,5-difluorophenyl)-1-(2-(5,5-dioxido-3-(trifluoromethyl)-6,7-dihydrothiopyrano[4,3-c]pyrazol-1(4H)-yl)acetamido)ethyl)pyridin-3-yl)-2-fluorobenzamide (**263**):

- 5 Compound **263** was prepared according to the method presented for the synthesis of Example 197 to provide 25 mg of title compound: ^1H NMR (400 MHz, cd_3od) δ 8.33 (d, 1H), 7.51 – 7.08 (m, 5H), 6.64 (t, 1H), 6.34 (d, 2H), 5.38 (dd, 1H), 4.95 – 4.81 (m, 2H), 4.19 (s, 2H), 3.57 – 3.43 (m, 1H), 3.31 (d, 2H), 3.17 – 2.94 (m, 3H). MS (m/z) 652 $[\text{M}+\text{H}]^+$.

10 Example 264

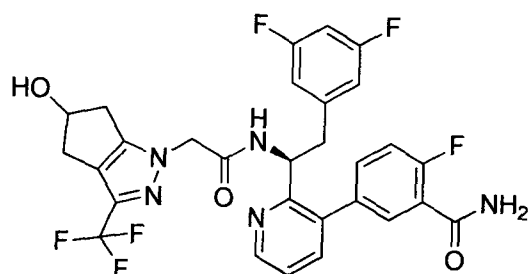
**264**

Synthesis of (S)-2-fluoro-5-(2-(2-(3-fluorophenyl)-1-(2-(3-oxo-3,4-dihydroquinoxalin-1(2H)-yl)acetamido)ethyl)pyridin-3-yl)benzamide (**264**):

- 15 Compound **264** was prepared according to the method presented for the synthesis of Example 59 utilizing **59D** and 2-(3-oxo-3,4-dihydroquinoxalin-1(2H)-yl)acetic acid to provide 18 mg of title compound: ^1H NMR (400 MHz, cd_3od) δ 8.73 – 8.59 (m, 1H), 7.63 (dd, 1H), 7.44 (ddd, 1H), 7.36 – 7.16 (m, 2H), 7.17 – 6.95 (m, 2H), 6.77 (t, 2H), 6.70 – 6.50 (m, 2H), 6.43 (dd, 2H), 5.29 (dd, 1H), 4.49 (d, 1H), 3.78 (s, 1H), 3.08 – 2.89 (m, 2H). MS (m/z) 542 $[\text{M}+\text{H}]^+$.

20

Example 265

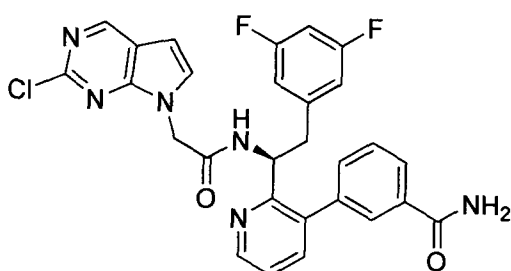
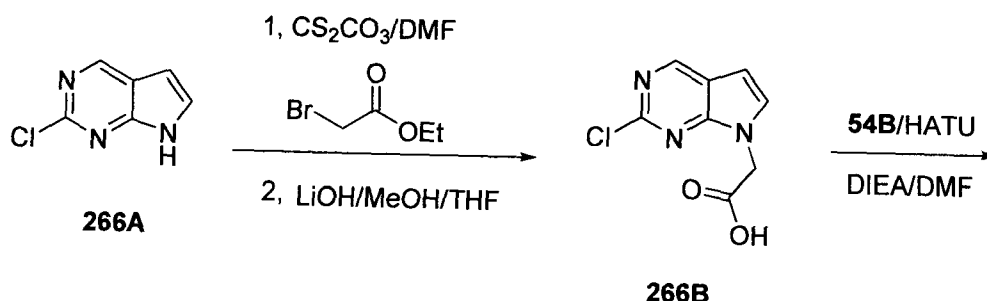
**265**

Synthesis of 5-(2-((1S)-2-(3,5-difluorophenyl)-1-(2-(5-hydroxy-3-(trifluoromethyl)-5,6-dihydrocyclopenta[c]pyrazol-1(4H)-yl)acetamido)ethyl)pyridin-3-yl)-2-fluorobenzamide (**265**):

Compound **265** was prepared according to the method presented for the synthesis of Example

- 5 325 substituting **237** for **325** to provide 19 mg of title compound: ^1H NMR (400 MHz, cd_3od) δ 8.71 (dd, 1H), 7.75 – 7.62 (m, 1H), 7.55 – 7.40 (m, 2H), 7.31 (s, 1H), 7.27 – 7.15 (m, 1H), 6.67 (td, 1H), 6.42 – 6.23 (m, 2H), 5.36 (td, 1H), 4.95 (ddd, 1H), 4.81 (d, 2H), 3.15 – 2.94 (m, 4H), 2.65 – 2.50 (m, 2H). MS (m/z) 604 [$\text{M}+\text{H}$] $^+$.

10 Example 266

**266C**

Synthesis of 2ethyl 2-(2-chloro-7H-pyrrolo[2,3-d]pyrimidin-7-yl)acetate (**266B**):

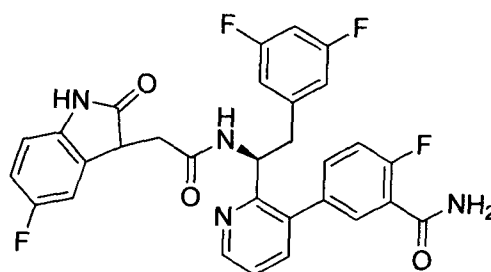
Compound **266B** was prepared according to the method presented for the synthesis of Example

- 74 substituting 2-chloro-7H-pyrrolo[2,3-d]pyrimidine (**266A**) for 1-7,8,8-trimethyl-3-(trifluoromethyl)-4,5,6,7-tetrahydro-1H-4,7-methanoindazole (**74A**) to provide 480 mg of title compound. MS (m/z) 240 [$\text{M}+\text{H}$] $^+$.

Synthesis of (S)-3-(2-(1-(2-(2-chloro-7H-pyrrolo[2,3-d]pyrimidin-7-yl)acetamido)-2-(3,5-difluorophenyl)ethyl)pyridin-3-yl)benzamide (**266C**):

Compound **266C** was prepared according to the method presented for the synthesis of Example 50 utilizing **50C** and 2-(2-chloro-7H-pyrrolo[2,3-d]pyrimidin-7-yl)acetic acid (**266B**) to provide 5 mg of title compound: ^1H NMR (400 MHz, cd_3od) δ 8.72 (d, 1H), 8.66 (dd, 1H), 7.78 (d, 1H), 7.68 (dd, 1H), 7.51 (s, 1H), 7.45 (dd, 1H), 7.41 – 7.30 (m, 2H), 7.22 (d, 1H), 6.67 – 6.50 (m, 2H), 6.18 (d, 2H), 5.36 (dd, 1H), 5.04 – 4.86 (m, 2H), 2.98 (d, 2H). MS (m/z) 547 $[\text{M}+\text{H}]^+$.

Example 267



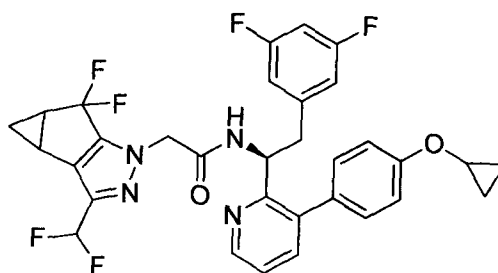
267

Synthesis of 5-(2-((1S)-2-(3,5-difluorophenyl)-1-(2-(5-fluoro-2-oxoindolin-3-yl)acetamido)ethyl)pyridin-3-yl)-2-fluorobenzamide (**267**):

Compound **267** was prepared according to the method presented for the synthesis of Example 54 utilizing **54B** and 2-(5-fluoro-2-oxoindolin-3-yl)acetic acid to provide 19 mg of title compound: ^1H NMR (400 MHz, cd_3od) δ 8.77 – 8.62 (m, 1H), 7.60 (dd, 1H), 7.53 – 7.31 (m, 2H), 7.31 – 7.21 (m, 1H), 7.20 – 6.97 (m, 1H), 6.96 – 6.77 (m, 2H), 6.65 (dd, 1H), 6.31 (t, 2H), 5.33 (dt, 1H), 3.90 (dt, 1H), 3.15 – 2.88 (m, 2H), 2.67 (dd, 2H).; MS (m/z) 563 $[\text{M}+\text{H}]^+$

20

Example 268

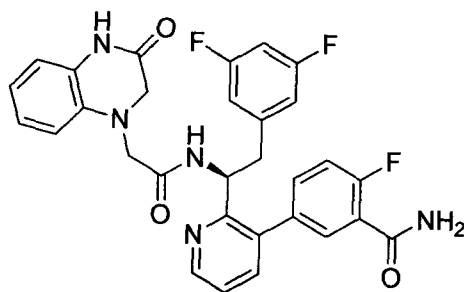


268

Synthesis of N-((S)-1-(3-(4-cyclopropoxyphenyl)pyridin-2-yl)-2-(3,5-difluorophenyl)ethyl)-2-(3-(difluoromethyl)-5,5-difluoro-3b,4,4a,5-tetrahydro-1H-cyclopropa[3,4]cyclopenta[1,2-c]pyrazol-1-yl)acetamide (**268**):

Compound 268 was prepared according to the method presented for the synthesis of Example 68 utilizing **68A** and (4-cyclopropoxyphenyl)boronic acid to provide 14 mg of title compound: ^1H NMR (400 MHz, cd_3od) δ 8.62 (d, 1H), 7.73 – 7.61 (m, 1H), 7.45 (dd, 1H), 7.10 – 6.95 (m, 4H), 6.68 (ddd, 2H), 6.25 (d, 2H), 5.49 (d, 1H), 3.79 (s, 1H), 2.97 (t, 2H), 2.46 (d, 2H), 1.36 (s, 1H), 1.07 (s, 1H), 0.86 – 0.65 (m, 4H). MS (m/z) 613 $[\text{M}+\text{H}]^+$.

10 Example 269

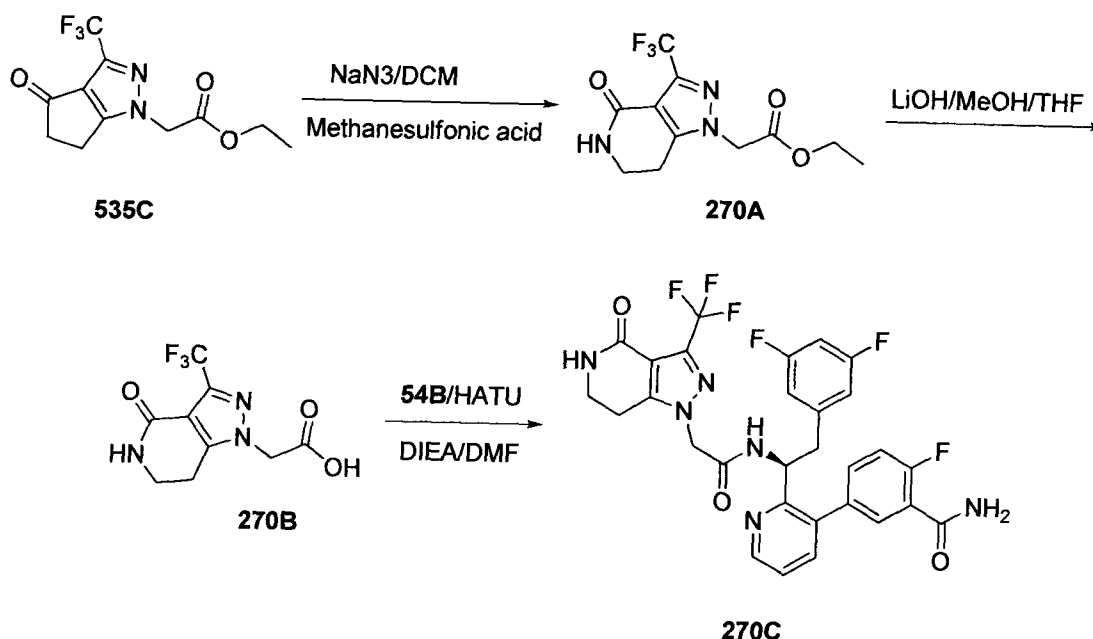


269

Synthesis of (S)-5-(2-(2-(3,5-difluorophenyl)-1-(2-(3-oxo-3,4-dihydroquinoxalin-1(2H)-yl)acetamido)ethyl)pyridin-3-yl)-2-fluorobenzamide (**269**):

Compound 269 was prepared according to the method presented for the synthesis of Example 54 utilizing **54B** and 2-(3-oxo-3,4-dihydroquinoxalin-1(2H)-yl)acetic acid to provide 14 mg of title compound: ^1H NMR (400 MHz, cd_3od) δ 8.79 – 8.70 (m, 1H), 7.89 – 7.68 (m, 2H), 7.63 – 7.33 (m, 4H), 7.30 – 7.13 (m, 2H), 6.85 (dd, 1H), 6.80 – 6.55 (m, 3H), 6.36 (d, 2H), 5.39 (dd, 1H), 4.60 (s, 1H), 3.87 (d, 1H), 3.19 – 2.99 (m, 2H). MS (m/z) 560 $[\text{M}+\text{H}]^+$.

20 Example 270



Synthesis of ethyl 2-(4-oxo-3-(trifluoromethyl)-4,5,6,7-tetrahydro-1H-pyrazolo[4,3-c]pyridin-1-yl)acetate (**270A**):

To a mixture of **535C** (200 mg, 0.72 mmol) in methanesulfonic acid (0.86 mL) and DCM (1.2 mL), sodium azide (65 mg, 1 mmol) was added and the mixture was stirred overnight. Diluted with DCM (30 mL) and washed with NaHCO₃(aq) twice. The organics were dried over Na₂SO₄, filtered and concentrated. The crude product was purified by SiO₂ chromatography eluting with a gradient of EtOAc in hexanes to provide 40 mg of title compound. MS (*m/z*) 292 [M+H]⁺.

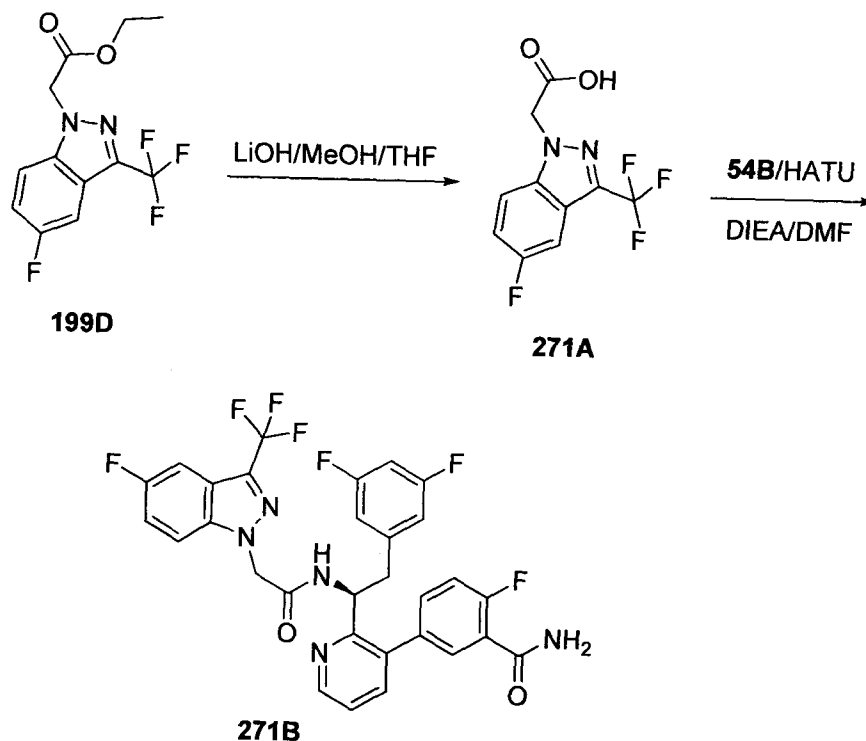
Synthesis of 2-(4-oxo-3-(trifluoromethyl)-4,5,6,7-tetrahydro-1H-pyrazolo[4,3-c]pyridin-1-yl)acetic acid (**270B**):

Compound **270B** was prepared according to the method presented for the synthesis of Example 74 substituting **270A** for **74B** to provide 30 mg of title compound. MS (*m/z*) 264 [M+H]⁺.

Synthesis of (S)-5-(2-(2-(3,5-difluorophenyl)-1-(2-(4-oxo-3-(trifluoromethyl)-4,5,6,7-tetrahydro-1H-pyrazolo[4,3-c]pyridin-1-yl)acetamido)ethyl)pyridin-3-yl)-2-fluorobenzamide (**270C**):

Compound **270C** was prepared according to the method presented for the synthesis of Example 54 utilizing **54B** and 2-(4-oxo-3-(trifluoromethyl)-4,5,6,7-tetrahydro-1H-pyrazolo[4,3-c]pyridin-1-yl)acetic acid to provide 42 mg of title compound: ¹H NMR (400 MHz, cd₃od) δ 8.72 (dd, 1H), 7.67 (dd, 1H), 7.47 (dd, 2H), 7.31 (s, 1H), 7.22 (dd, 1H), 6.76 – 6.60 (m, 1H), 6.34 (d, 2H), 5.36 (t, 1H), 4.95 (s, 2H), 3.52 (t, 2H), 3.10 (t, 2H), 2.96 – 2.77 (m, 2H). MS (*m/z*) 617 [M+H]⁺.

Example 271



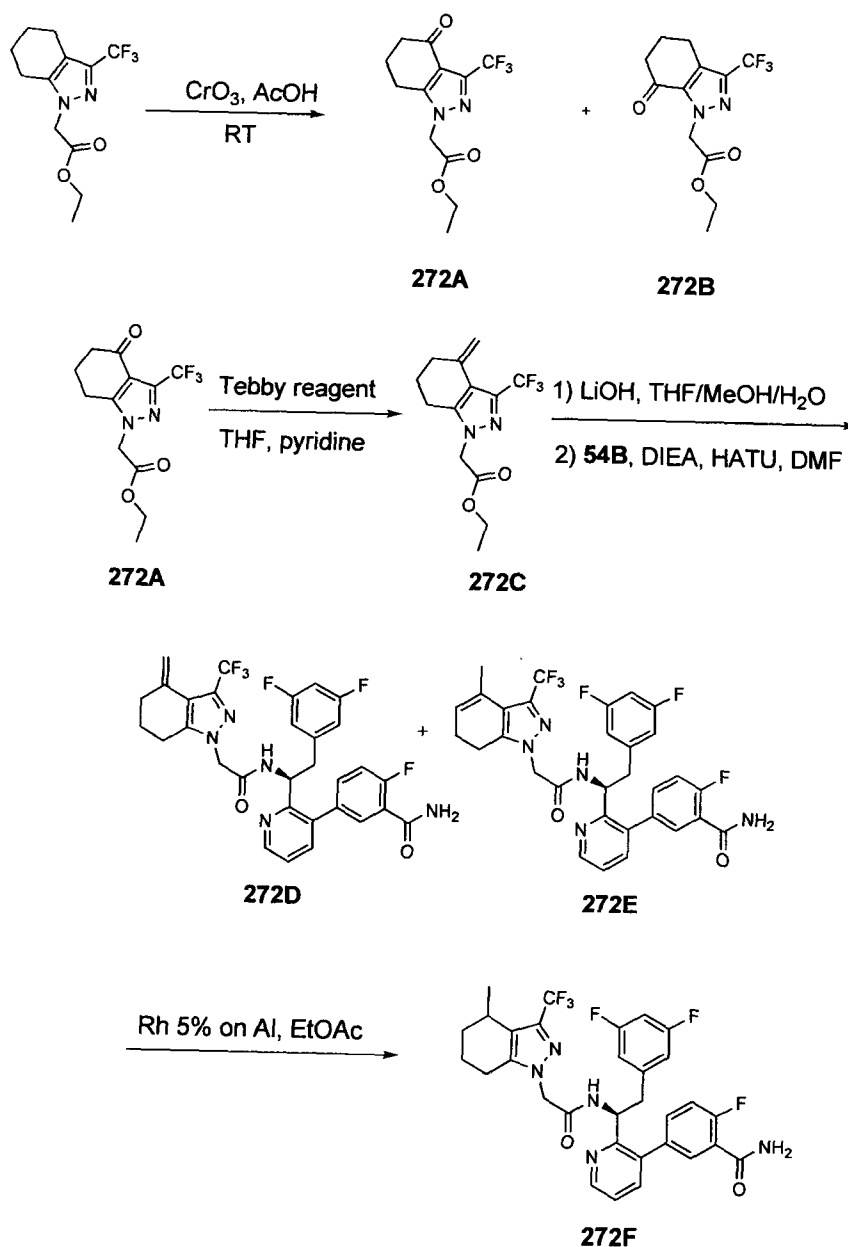
Synthesis of 2-(5-fluoro-3-(trifluoromethyl)-1H-indazol-1-yl)acetic acid (**271A**):

- 5 Compound 271A was prepared according to the method presented for the synthesis of Example 74 substituting **199D** for **74B** to provide 52.6 mg of title compound. MS (m/z) 263 [$M+H$]⁺.

Synthesis of (S)-5-(2-(2-(3,5-difluorophenyl)-1-(2-(5-fluoro-3-(trifluoromethyl)-1H-indazol-1-yl)acetamido)ethyl)pyridin-3-yl)-2-fluorobenzamide (**271B**):

- 10 Compound 271B was prepared according to the method presented for the synthesis of Example 54 utilizing **54B** and **271A** to provide 76 mg of title compound: ¹H NMR (400 MHz, cd_3od) δ 8.72 (dd, 1H), 7.67 (dd, 1H), 7.55 (dd, 1H), 7.52 – 7.38 (m, 3H), 7.38 – 7.24 (m, 2H), 7.19 (dd, 1H), 6.66 (ddd, 1H), 6.33 (t, 2H), 5.36 (t, 1H), 5.24 (s, 2H), 3.08 (d, 2H). MS (m/z) 616 [$M+H$]⁺.

15 Example 272



Synthesis of ethyl 2-(4-oxo-3-(trifluoromethyl)-4,5,6,7-tetrahydro-1H-indazol-1-yl)acetate (**272A**):

- 5 Ethyl 2-(3-(trifluoromethyl)-4,5,6,7-tetrahydro-1H-indazol-1-yl)acetate (4.9 g, 17.7 mmol) was dissolved in 170 mL of acetic acid. To it was added chromium trioxide (2.65 g, 26.5 mmol) and the resulting mixture was stirred at ambient temperature for 3 days. To it was added more chromium trioxide (885 mg, 8.85 mmol) and the reaction was allowed to stir for one day. It was
- 10 partitioned between EtOAc and water. The organic layer was separated, washed with half brine, dried over MgSO_4 and filtered. The filtrate was concentrated and purified by silica gel

chromatography eluting with EtOAc and hexanes to afford 1.78 g of **272B** and 1.94 g of the title compound. MS (m/z) 291.16 [M+H]⁺.

Synthesis of ethyl 2-(4-methylene-3-(trifluoromethyl)-4,5,6,7-tetrahydro-1H-indazol-1-yl)acetate (**272C**):

Ethyl 2-(4-oxo-3-(trifluoromethyl)-4,5,6,7-tetrahydro-1H-indazol-1-yl)acetate (600 mg, 2 mmol) was dissolved in 20 mL of THF and 4 mL of pyridine. To it at 0 °C was slowly added 2 mL of Tebbe reagent (0.5 M in toluene, 3 mmol) and the reaction mixture was stirred at ambient temperature for 3 hours. More Tebbe reagent (0.5 M in toluene, 3 mmol) was added and the reaction was allowed to stir for 3 days. It was quenched at 0 °C with NaHCO₃ (saturated aqueous solution), and filtered through a pad of celite. The filtrate was partitioned between EtOAc and water. The organic layer was separated, washed with half brine, dried over MgSO₄ and filtered. The filtrate was concentrated and purified by silica gel chromatography eluting with EtOAc and hexanes to afford 45 mg of the title compound. MS (m/z) 289.10 [M+H]⁺.

Synthesis of (S)-5-(2-(2-(3,5-difluorophenyl)-1-(2-(4-methylene-3-(trifluoromethyl)-4,5,6,7-tetrahydro-1H-indazol-1-yl)acetamido)ethyl)pyridin-3-yl)-2-fluorobenzamide (**272D**) and (S)-5-(2-(2-(3,5-difluorophenyl)-1-(2-(4-methyl-3-(trifluoromethyl)-6,7-dihydro-1H-indazol-1-yl)acetamido)ethyl)pyridin-3-yl)-2-fluorobenzamide (**272E**):

The mixture of Compound **272D** and Compound **272E** was prepared according to the method presented in the synthesis of Example 60 utilizing Compound **54B** and ethyl 2-(4-methylene-3-(trifluoromethyl)-4,5,6,7-tetrahydro-1H-indazol-1-yl)acetate to afford the title compounds. MS (m/z) 614.22 [M+H]⁺.

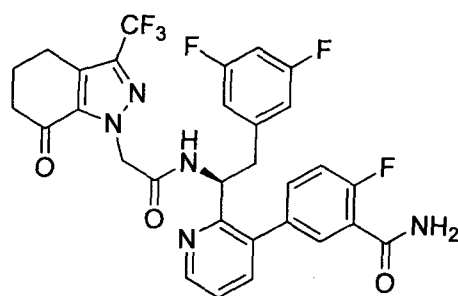
Synthesis of 5-(2-((1S)-2-(3,5-difluorophenyl)-1-(2-(4-methyl-3-(trifluoromethyl)-4,5,6,7-tetrahydro-1H-indazol-1-yl)acetamido)ethyl)pyridin-3-yl)-2-fluorobenzamide (**272F**):

The mixture of **272D** and **272E** (7.2 mg) was dissolved in 10 mL of EtOAc. The system was purged with argon, and then Rh/Al (5%, 5 mg) was added. The reaction was stirred under 1 atm H₂ at ambient temperature for 16 hours. Upon completion of the reaction, it was filtered through a pad of celite and washed with EtOAc. The filtrate was collected and the volatiles were removed in vacuo. The residue was purified by reverse phase HPLC eluting with acetonitrile/water (with 0.1% TFA) to afford 3.4 mg of the title compound. MS (m/z) 616.19 [M+H]⁺. ¹H NMR (400 MHz, cd₃od) δ 8.61 (dd, J = 4.8, 1.5 Hz, 1H), 7.55 (dd, J = 7.8, 1.5 Hz,

1H), 7.42 – 7.33 (m, 2H), 7.27 (s, 1H), 7.15 (dd, J = 10.7, 8.5 Hz, 1H), 6.59 (t, J = 9.1 Hz, 1H), 6.27 (d, J = 8.1 Hz, 2H), 5.29 (t, J = 7.5 Hz, 1H), 4.70 (s, 2H), 2.98 (d, J = 8.1 Hz, 2H), 2.85 (d, J = 5.8 Hz, 1H), 2.47 – 2.14 (m, 2H), 1.92 – 1.63 (m, 3H), 1.54 – 1.43 (m, 1H), 1.10 (d, J = 6.9 Hz, 3H).

5

Example 273



273

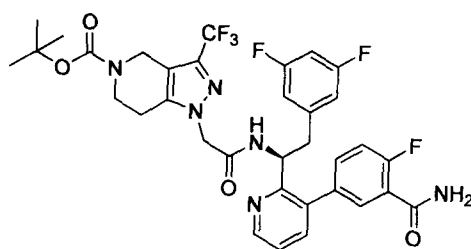
- 10 Synthesis of (S)-5-(2-(2-(3,5-difluorophenyl)-1-(2-(7-oxo-3-(trifluoromethyl)-4,5,6,7-tetrahydro-1H-indazol-1-yl)acetamido)ethyl)pyridin-3-yl)-2-fluorobenzamide (**273**):

Compound 273 was prepared (11 mg) according to the method presented in the synthesis of Example 60 utilizing Compound 54B and Compound 272B to provide the title compound: MS

- 15 (m/z) 616.43 [M+H]⁺. ¹H NMR (400 MHz, cd₃od) δ 8.75 (dd, J = 5.0, 1.6 Hz, 1H), 7.73 (dd, J = 7.8, 1.6 Hz, 1H), 7.53 (dd, J = 7.8, 5.0 Hz, 1H), 7.45 – 7.28 (m, 2H), 7.20 (dd, J = 10.7, 8.6 Hz, 1H), 6.66 (tt, J = 9.2, 2.3 Hz, 1H), 6.31 (d, J = 6.1 Hz, 2H), 5.36 (dd, J = 8.4, 6.7 Hz, 1H), 5.24 (s, 2H), 3.18 – 3.02 (m, 2H), 2.85 (t, J = 5.9 Hz, 2H), 2.60 – 2.47 (m, 2H), 2.25 – 2.03 (m, 2H).

Example 274

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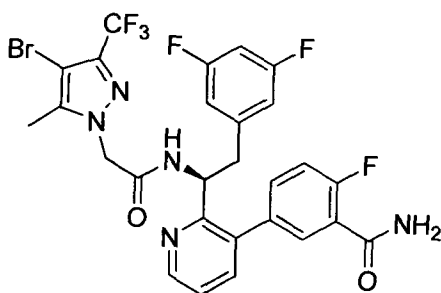


274

Synthesis of (S)-tert-butyl 1-(2-(1-(3-(3-carbamoyl-4-fluorophenyl)pyridin-2-yl)-2-(3,5-difluorophenyl)ethylamino)-2-oxoethyl)-3-(trifluoromethyl)-6,7-dihydro-1H-pyrazolo[4,3-c]pyridine-5(4H)-carboxylate (**274**):

Compound 274 was prepared (7 mg) according to the method presented in the synthesis of Example 56 utilizing 56A and tert-butyl 3-(trifluoromethyl)-6,7-dihydro-1H-pyrazolo[4,3-c]pyridine-5(4H)-carboxylate to provide the title compound. MS (m/z) 703.16 [M+H]⁺. ¹H NMR (400 MHz, cdcl₃) δ 8.56 (d, J = 4.8 Hz, 1H), 7.64 (d, J = 5.7 Hz, 1H), 7.48 (d, J = 7.0 Hz, 1H), 7.38 (s, 1H), 7.33 – 7.28 (m, 1H), 7.18 (dd, J = 11.1, 8.5 Hz, 1H), 6.77 (s, 1H), 6.54 (t, J = 9.1 Hz, 1H), 6.11 (d, J = 6.1 Hz, 2H), 5.86 (s, 1H), 5.42 (dd, J = 14.9, 7.7 Hz, 1H), 4.70 (s, 2H), 4.51 (s, 2H), 3.69 (s, 2H), 2.85 (dd, J = 16.0, 8.2 Hz, 2H), 2.61 (d, J = 5.3 Hz, 2H), 1.48 (d, J = 7.8 Hz, 9H).

Example 275

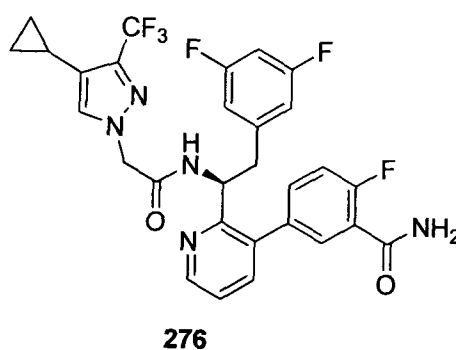


275

Synthesis of (S)-5-(2-(1-(2-(4-bromo-5-methyl-3-(trifluoromethyl)-1H-pyrazol-1-yl)acetamido)-2-(3,5-difluorophenyl)ethyl)pyridin-3-yl)-2-fluorobenzamide (**275**):

Compound 275 was prepared (6 mg) according to the method presented in the synthesis of Example 56 utilizing Compound 56A and 4-bromo-5-methyl-3-(trifluoromethyl)-1H-pyrazole to provide the title compound. MS (m/z) 641.32 [M+H]⁺. ¹H NMR (400 MHz, cd₃od) δ 8.69 (dd, J = 4.7, 1.6 Hz, 1H), 7.56 (dd, J = 7.8, 1.7 Hz, 1H), 7.46 – 7.27 (m, 3H), 7.21 (dd, J = 10.7, 8.5 Hz, 1H), 6.65 (t, J = 9.2 Hz, 1H), 6.32 (d, J = 6.3 Hz, 2H), 5.40 – 5.25 (m, 1H), 4.92 (s, 2H), 3.06 (qd, J = 13.3, 7.8 Hz, 2H), 2.17 (s, 3H).

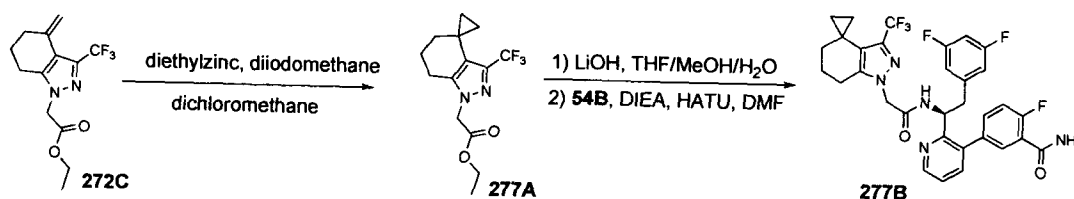
Example 276



Synthesis of (S)-5-(2-(1-(2-(4-cyclopropyl-3-(trifluoromethyl)-1H-pyrazol-1-yl)acetamido)-2-(3,5-difluorophenyl)ethyl)pyridin-3-yl)-2-fluorobenzamide (**276**):

To the mixture of (S)-5-(2-(1-(2-(4-bromo-3-(trifluoromethyl)-1H-pyrazol-1-yl)acetamido)-2-(3,5-difluorophenyl)ethyl)pyridin-3-yl)-2-fluorobenzamide (**463**, 20 mg, 0.03 mmol), cyclopropane boronic acid (8.2 mg, 0.09 mmol) and potassium phosphate tribasic (25 mg, 0.12 mmol) were added 1 mL of toluene and 2 drops of water. After the system was purged with argon, palladium (II) acetate (2 mg, 0.003 mmol) and tricyclohexylphosphine (2 mg, 0.006 mmol) was added and the reaction mixture was heated up to 120 °C for 3 hours. The solvent was removed and the residue was purified by reverse phase HPLC eluting with acetonitrile/water (with 0.1% TFA) to afford 6.5 mg of the title compound. MS (m/z) 588.35 [M+H]⁺. ¹H NMR (400 MHz, cd₃od) δ 8.68 (dd, J = 4.8, 1.6 Hz, 1H), 7.64 (dd, J = 7.8, 1.6 Hz, 1H), 7.49 – 7.29 (m, 4H), 7.22 (dd, J = 10.7, 8.5 Hz, 1H), 6.65 (t, J = 9.2 Hz, 1H), 6.30 (d, J = 6.3 Hz, 2H), 5.33 (t, J = 7.5 Hz, 1H), 4.83 (s, 1H), 3.04 (d, J = 7.7 Hz, 2H), 1.72 (m, 1H), 1.01 – 0.76 (m, 2H), 0.62 – 0.45 (m, 2H).

Example 277



Synthesis of ethyl 2-(3'-(trifluoromethyl)-6',7'-dihydrospiro[cyclopropane-1,4'-indazole]-1'(5'H)-yl)acetate (**277A**):

Dichloromethane (3 mL) was added to diethylzinc (1.0 M hexane solution, 1.56 mL, 1.56

mmol), and then a solution of TFA (48 μL, 0.6 mmol) in dichloromethane (2 mL) was slowly

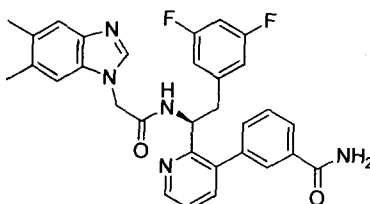
added at 0 °C. The reaction mixture was stirred for 20 min, and then a solution of diiodomethane (125 µL, 1.5 mmol) in dichloromethane (2 mL) was added dropwise. The reaction mixture was stirred for 20 min, and then a solution of ethyl 2-(4-methylene-3-(trifluoromethyl)-4,5,6,7-tetrahydro-1H-indazol-1-yl)acetate (**272**, 45 mg, 0.15 mmol) in dichloromethane (1.5 mL) was added and the reaction was allowed to stir at ambient temperature for 16 hours.

Dichloromethane and saturated aqueous ammonium chloride solution were added to the reaction mixture and the organic layer was separated and the aqueous layer was extracted by dichloromethane one more time. The combined organic layer was dried over sodium sulfate anhydrous, filtered and concentrated. The residue was purified by silica gel chromatography eluting with EtOAc and hexane to afford 21 mg of the title compound. MS (m/z) 303.20 [M+H]⁺.

Synthesis of (S)-5-(2-(2-(3,5-difluorophenyl)-1-(2-(3'-(trifluoromethyl)-6',7'-dihydrospiro[cyclopropane-1,4'-indazole]-1'(5'H)-yl)acetamido)ethyl)pyridin-3-yl)-2-fluorobenzamide (**277B**):

Compound **277B** was prepared (27 mg) according to the method presented in the synthesis of Example 60 utilizing Compound **54B** and ethyl 2-(3'-(trifluoromethyl)-6',7'-dihydrospiro[cyclopropane-1,4'-indazole]-1'(5'H)-yl)acetate to provide the title compound. MS (m/z) 628.5 [M+H]⁺. ¹H NMR (400 MHz, cd₃od) δ 8.71 (dd, J = 4.9, 1.6 Hz, 1H), 7.71 (dd, J = 7.8, 1.6 Hz, 1H), 7.48 (ddd, J = 9.2, 7.3, 3.6 Hz, 2H), 7.37 (s, 1H), 7.24 (dd, J = 10.7, 8.5 Hz, 1H), 6.68 (tt, J = 9.2, 2.2 Hz, 1H), 6.36 (t, J = 6.2 Hz, 2H), 5.38 (t, J = 7.6 Hz, 1H), 4.79 (s, 2H), 3.21 – 2.94 (m, 2H), 2.63 – 2.39 (m, 2H), 2.02 – 1.76 (m, 2H), 1.64 – 1.42 (m, 2H), 1.08 – 0.87 (m, 2H), 0.63 (t, J = 5.2 Hz, 2H).

Example 278

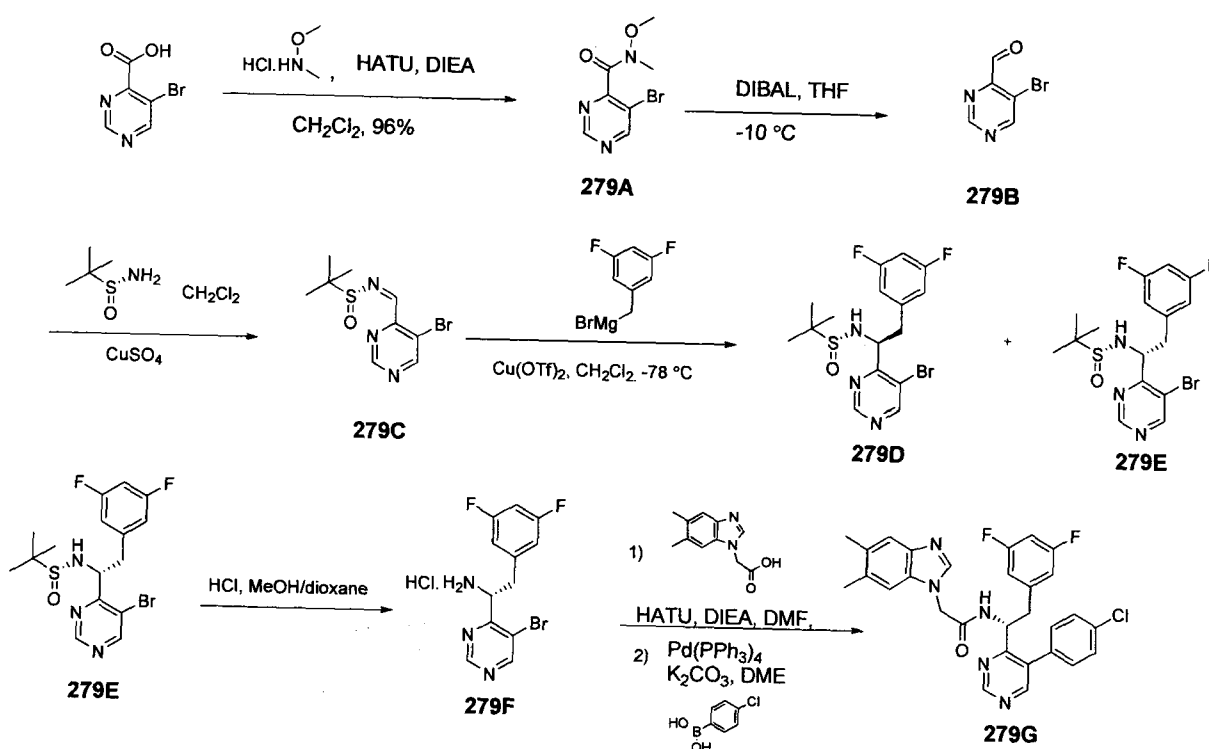


278

Synthesis of (S)-3-(2-(2-(3,5-difluorophenyl)-1-(2-(5,6-dimethyl-1H-benzo[d]imidazol-1-yl)acetamido)ethyl)pyridin-3-yl)benzamide (**278**):

Compound **278** was prepared (13 mg) according to the method presented in the synthesis of Example 55 utilizing Compound **55D** and 2-(5,6-dimethyl-1H-benzo[d]imidazol-1-yl)acetic acid, and then Suzuki coupling with 3-carbamoylphenylboronic acid to afford the title compound. MS (m/z) 540.2 $[M+H]^+$. 1H NMR (400 MHz, cd_3od) δ 9.23 (s, 1H), 8.74 (d, $J = 4.8$ Hz, 1H), 7.87 (d, $J = 7.7$ Hz, 1H), 7.71 – 7.55 (m, 3H), 7.53 – 7.39 (m, 3H), 7.29 (d, $J = 7.7$ Hz, 1H), 6.66 (m, 1H), 6.30 (d, $J = 6.4$ Hz, 2H), 5.45 (t, $J = 7.5$ Hz, 1H), 5.26 (s, 2H), 3.18 – 2.96 (m, 2H), 2.44 (d, $J = 6.9$ Hz, 6H).

Example 279



Synthesis of 5-bromo-N-methoxy-N-methylpyrimidine-4-carboxamide (**279A**):

5-bromopyrimidine-4-carboxylic acid (5 g, 24.6 mmol) and N,O-dimethylhydroxylamine hydrochloride (3.6 g, 36.9 mmol) were dissolved in 100 mL of CH_2Cl_2 and to it was added N,N-diisopropylethylamine (21 mL, 123 mmol). The reaction mixture was cooled down to 0 °C and to it was added HATU (11.2 g, 29.5 mmol). The reaction mixture was allowed to stir at 0 °C for 30 min. it was then diluted with CH_2Cl_2 and washed with half brine. The organic layer was separated, dried over $MgSO_4$, filtered and concentrated. The crude product was purified by silica

gel chromatography eluting with EtOAc/hexanes to afford 5.84 g of the title compound. MS (m/z): 248.1 $[M+H]^+$.

Synthesis of 5-bromopyrimidine-4-carbaldehyde (**279B**):

5 5-bromo-N-methoxy-N-methylpyrimidine-4-carboxamide (2.45 g, 10 mmol) was dissolved in 50 mL of THF and cooled down to -10 °C. DIBAL (1.0 M in toluene, 15 mL, and 15 mmol) was added slowly to keep internal temperature at -10 °C. After addition, the reaction was quenched with iPrOH and 1N HCl. The mixture was partitioned between EtOAc and brine. The organic layer was separated, dried over $MgSO_4$, filtered and concentrated to afford 1.19 g of the title
10 compound. MS (m/z): 187.2 $[M+H]^+$.

Synthesis of N-((5-bromopyrimidin-4-yl)methylene)-2-methylpropane-2-sulfinamide (**279C**):

Compound **279C** was prepared according to the method presented for the synthesis of Example 13C substituting Compound **279B** for 3-(4-methoxyphenyl)picolinaldehyde to provide the title
15 compound: MS (m/z) 292.0 $[M+H]^+$.

Synthesis of (R)-N-((R)-1-(5-bromopyrimidin-4-yl)-2-(3,5-difluorophenyl)ethyl)-2-methylpropane-2-sulfinamide (**279E**):

(3,5-difluorobenzyl)magnesium bromide (0.25 M in ether, 20 mL, 5 mmol) was added dropwise
20 to a solution of N-((5-bromopyrimidin-4-yl)methylene)-2-methylpropane-2-sulfinamide (730 mg, 2.5 mmol) and copper (II) triflate (45 mg, 0.125 mmol) in CH_2Cl_2 (15 mL) at -78 °C. After addition, ammonium chloride (aq, 10 mL) was added to the reaction and the mixture was allowed to warm up to ambient temperature. It was extracted with EtOAc (2x30mL). The organic layer was dried over Na_2SO_4 , filtered and concentrated. The crude product was purified by flash
25 column to afford 136 mg of (R)-N-((S)-1-(5-bromopyrimidin-4-yl)-2-(3,5-difluorophenyl)ethyl)-2-methylpropane-2-sulfinamide (**279D**) and 355 mg of the title compound: MS (m/z) 419.8 $[M+H]^+$

Synthesis of (R)-1-(5-bromopyrimidin-4-yl)-2-(3,5-difluorophenyl)ethanamine hydrochloride (**279F**):
30

(R)-N-((R)-1-(5-bromopyrimidin-4-yl)-2-(3,5-difluorophenyl)ethyl)-2-methylpropane-2-sulfinamide (766 mg, 1.8 mmol) was dissolved in 5 mL of methanol and to it was added HCl solution (4N in dioxane, 1.8 mL). After stirring at ambient temperature for 10 min, diethyl ether

was added and the mixture was allowed to stir for 1 hour. The resulting precipitate was collected by vacuum filtration and then dried under high vacuum to provide 554 mg of the title compound: MS (m/z) 316.2 [M+H]⁺.

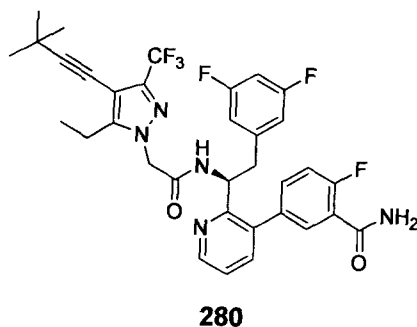
5 Synthesis (R)-N-(1-(5-(4-chlorophenyl)pyrimidin-4-yl)-2-(3,5-difluorophenyl)ethyl)-2-(5,6-dimethyl-1H-benzo[d]imidazol-1-yl)acetamide (**279G**):

Compound 279G was prepared (11 mg) according to the method presented in the synthesis of Example 57 utilizing Compound 279F and 2-(5,6-dimethyl-1H-benzo[d]imidazol-1-yl)acetic acid, and then Suzuki coupling with 4-chlorophenylboronic acid to afford the title compound.

10 MS (m/z) 532.3 [M+H]⁺. ¹H NMR (400 MHz, cd₃od) δ 9.23 (d, *J* = 15.1 Hz, 2H), 8.54 (s, 1H), 7.59 (s, 1H), 7.51 – 7.35 (m, 3H), 7.18 (d, *J* = 8.1 Hz, 2H), 6.74 (m, 1H), 6.38 (d, *J* = 6.8 Hz, 2H), 5.45 (d, *J* = 7.5 Hz, 1H), 5.25 (s, 2H), 3.08 (t, *J* = 7.1 Hz, 2H), 2.45 (s, 6H).

Example 280:

15



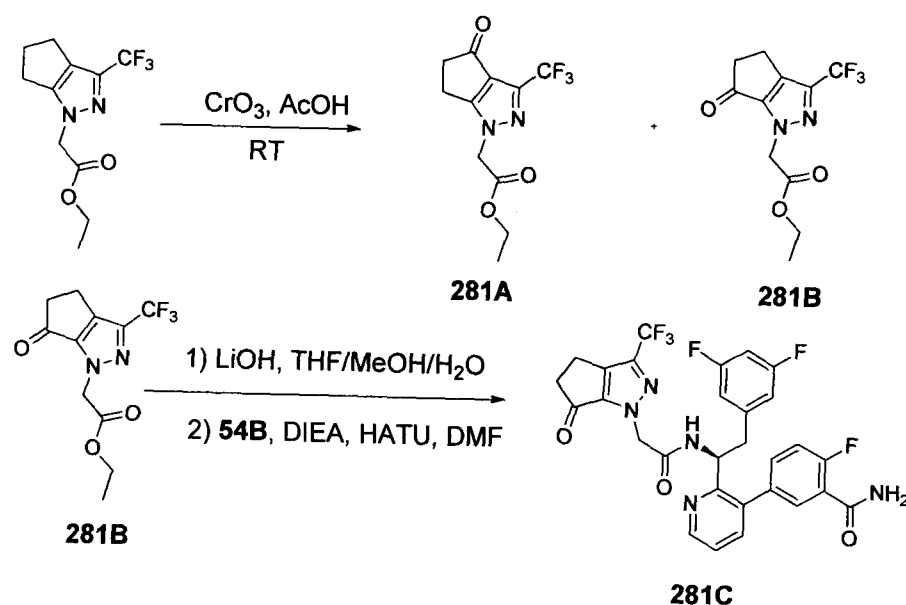
Synthesis of (S)-5-(2-(2-(3,5-difluorophenyl)-1-(2-(4-(3,3-dimethylbut-1-ynyl)-5-ethyl-3-(trifluoromethyl)-1H-pyrazol-1-yl)acetamido)ethyl)pyridin-3-yl)-2-fluorobenzamide (**280**):

20 (S)-5-(2-(1-(2-(4-bromo-5-ethyl-3-(trifluoromethyl)-1H-pyrazol-1-yl)acetamido)-2-(3,5-difluorophenyl)ethyl)pyridin-3-yl)-2-fluorobenzamide (**58**, 40 mg, 0.06 mmol) was dissolved in 2 mL of DMF and 0.4 mL of triethylamine. The system was degassed and purged with argon. To it was added copper(I) iodide (2.2 mg, 0.012mmol) and bis(triphenylphosphine)palladium(II) chloride (4.2 mg, 0.006 mmol). The system was purged with argon again. 3,3-dimethylbut-1-yne

25 (37 μL, 0.3 mmol) was added and the mixture was heated up to 85 °C for 16 hours and then added more 3,3-dimethylbut-1-yne (74 μL, 0.6 mmol), copper(I) iodide (2.2 mg, 0.012mmol) and bis(triphenylphosphine)palladium(II) chloride(4.2 mg, 0.006 mmol). The mixture was heated up to 180 °C for 16 hours. It was cooled down and filtered through a pad of celite and

washed with EtOAc. The filtrate was washed with 5% LiCl aqueous solution, water (20 mL with 1 mL of ammonia) and brine. The organic layer was separated, washed with half brine, dried over MgSO₄ and filtered. The filtrate was concentrated and purified by reverse phase HPLC eluting with acetonitrile/water (with 0.1% TFA) to afford 6 mg of the title compound. MS (*m/z*) 657.10 [M+H]⁺. ¹H NMR (400 MHz, cd₃od) δ 8.69 (dd, *J* = 4.8, 1.6 Hz, 1H), 7.60 (dd, *J* = 7.8, 1.6 Hz, 1H), 7.41 (dd, *J* = 7.8, 4.8 Hz, 2H), 7.31 (s, 1H), 7.21 (dd, *J* = 10.7, 8.5 Hz, 1H), 6.66 (t, *J* = 9.2 Hz, 1H), 6.33 (d, *J* = 6.3 Hz, 2H), 5.34 (t, *J* = 7.5 Hz, 1H), 4.86 (s, 2H), 3.13 – 2.96 (m, 2H), 2.60 (q, *J* = 7.6 Hz, 2H), 1.27 (s, 9H), 1.13 (t, *J* = 7.6 Hz, 3H).

10 Example 281



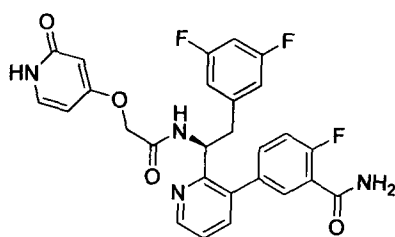
15 Synthesis of ethyl 2-(6-oxo-3-(trifluoromethyl)-5,6-dihydrocyclopenta[c]pyrazol-1(4H)-yl)acetate (**281B**):

Compound 281B was prepared according to the method presented in the synthesis of Example 272B utilizing ethyl 2-(3-(trifluoromethyl)-5,6-dihydrocyclopenta[c]pyrazol-1(4H)-yl)acetate to afford the title compound; MS (*m/z*) 277.06 [M+H]⁺.

20 Synthesis of (S)-5-(2-(2-(3,5-difluorophenyl)-1-(2-(6-oxo-3-(trifluoromethyl)-5,6-dihydrocyclopenta[c]pyrazol-1(4H)-yl)acetamido)ethyl)pyridin-3-yl)-2-fluorobenzamide (**281C**):

Compound 281C was prepared (12 mg) according to the method presented in the synthesis of Example 54 utilizing Compound 54B and ethyl 2-(6-oxo-3-(trifluoromethyl)-5,6-dihydrocyclopenta[c]pyrazol-1(4H)-yl)acetate to provide the title compound ; MS (m/z) 602.49 $[M+H]^+$. 1H NMR (400 MHz, cd_3od) δ 8.73 (dd, $J = 4.9, 1.6$ Hz, 1H), 7.67 (dd, $J = 7.8, 1.6$ Hz, 1H), 7.48 (dd, $J = 7.8, 4.9$ Hz, 1H), 7.38 (d, $J = 6.8$ Hz, 1H), 7.31 (s, 1H), 7.20 (dd, $J = 10.7, 8.5$ Hz, 1H), 6.73 – 6.57 (m, 1H), 6.30 (d, $J = 6.1$ Hz, 2H), 5.36 (t, $J = 7.6$ Hz, 1H), 5.12 – 4.98 (m, 2H), 3.08 (d, $J = 7.6$ Hz, 2H), 3.03 (dd, $J = 6.3, 3.4$ Hz, 2H), 2.99 – 2.89 (m, 2H).

Example 282

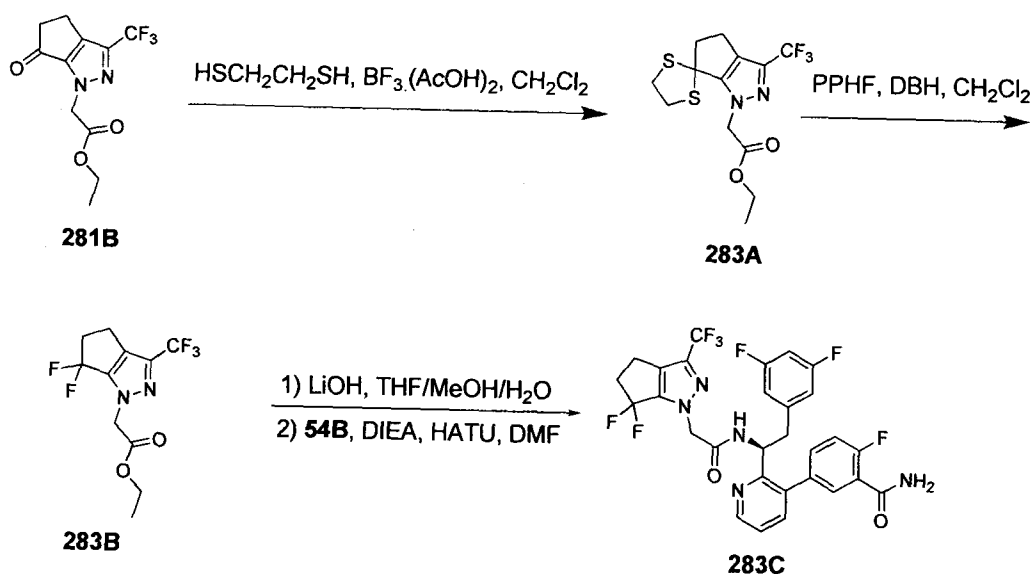


282

Synthesis of (S)-5-(2-(2-(3,5-difluorophenyl)-1-(2-(2-oxo-1,2-dihydropyridin-4-yloxy)acetamido)ethyl)pyridin-3-yl)-2-fluorobenzamide (**282**):

(S)-5-(2-(1-(2-(2-chloropyridin-4-yloxy)acetamido)-2-(3,5-difluorophenyl)ethyl)pyridin-3-yl)-2-fluorobenzamide (**332**, 25 mg) was dissolved in 1 mL of acetic acid and heated up to 150 °C in a Biotage® Initiator Microwave Synthesizer for 75 min. It was cooled down and the solvent was removed. The residue was purified by reverse phase HPLC eluting with acetonitrile/water (with 0.1% TFA) to afford 5 mg of the title compound. MS (m/z) 523.27 $[M+H]^+$. 1H NMR (400 MHz, cd_3od) δ 8.61 (dd, $J = 4.8, 1.6$ Hz, 1H), 7.56 (dd, $J = 7.8, 1.6$ Hz, 1H), 7.46 – 7.29 (m, 3H), 7.26 (s, 1H), 7.17 (dd, $J = 10.7, 8.6$ Hz, 1H), 6.59 (t, $J = 9.2$ Hz, 1H), 6.23 (dd, $J = 9.5, 4.5$ Hz, 3H), 5.85 (d, $J = 2.4$ Hz, 1H), 5.34 (t, $J = 7.5$ Hz, 1H), 4.52 (s, 2H), 2.96 (t, $J = 21.2$ Hz, 2H).

Example 283



Synthesis of ethyl 2-(3-(trifluoromethyl)-4,5-dihydro-1H-spiro[cyclopenta[c]pyrazole-6,2'-[1,3]dithiolane]-1-yl)acetate (**283A**):

- 5 To a solution of ethyl 2-(6-oxo-3-(trifluoromethyl)-5,6-dihydrocyclopenta[c]pyrazol-1(4H)-yl)acetate (**281B**, 219mg, 0.79 mmol) in CH_2Cl_2 (2 mL) was added 1,2-ethanedithiol (100 μL , 1.2 mmol) and $\text{BF}_3 \cdot 2\text{AcOH}$ (165 μL , 1.2 mmol) under N_2 . The mixture was stirred at ambient temperature for 16 hours. The reaction was quenched with saturated NaHCO_3 aqueous solution at 0 °C; and then extracted with EtOAc. The organic layer was separated, dried over MgSO_4 ,
 10 filtered and concentrated. The residue was purified by silica gel chromatography eluting with EtOAc/Hexanes to afford 253 mg of the title compound: MS (m/z) 353.17 [$\text{M}+\text{H}$] $^+$.

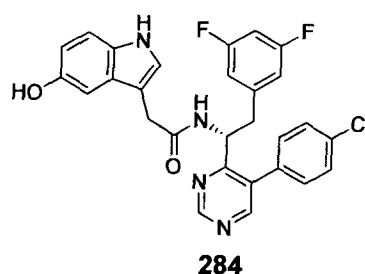
Synthesis of ethyl 2-(6,6-difluoro-3-(trifluoromethyl)-5,6-dihydrocyclopenta[c]pyrazol-1(4H)-yl)acetate (**283B**):

- 15 In a Teflon vessel was added 1,3-dibromo-5,5-dimethylhydantoin (114 mg, 0.4 mmol) and CH_2Cl_2 (1 mL). The mixture was allowed to stir under N_2 and cooled down to -78 °C. To it was added 1 mL of hydrogen fluoride pyridine (pyridine ~30%, hydrogen fluoride ~70%) followed by dropwise addition of a solution of ethyl 2-(3-(trifluoromethyl)-4,5-dihydro-1H-spiro[cyclopenta[c]pyrazole-6,2'-[1,3]dithiolane]-1-yl)acetate (141 mg, 0.4 mmol) in CH_2Cl_2 (1
 20 mL). The reaction was kept at -78 °C for 30 min, and then warmed up to -30 °C. The reaction was carefully poured to cold (0 °C) saturated NaHCO_3 , and added more NaHCO_3 if pH was less than 7. Then it was extracted with CH_2Cl_2 . The organic layer was separated, dried over MgSO_4 , filtered and concentrated. The residue was purified by silica gel chromatography eluting with EtOAc/Hexanes to afford 40 mg of the title compound: MS (m/z) 298.97, [$\text{M}+\text{H}$] $^+$.

Synthesis of (S)-5-(2-(1-(2-(6,6-difluoro-3-(trifluoromethyl)-5,6-dihydrocyclopenta[c]pyrazol-1(4H)-yl)acetamido)-2-(3,5-difluorophenyl)ethyl)pyridin-3-yl)-2-fluorobenzamide (**283C**):

Compound 283C was prepared (30 mg) according to the method presented in the synthesis of Example 54 utilizing Compound 54B and ethyl 2-(6,6-difluoro-3-(trifluoromethyl)-5,6-dihydrocyclopenta[c]pyrazol-1(4H)-yl)acetate to provide the title compound ; MS (m/z) 624.48 $[M+H]^+$. 1H NMR (400 MHz, cd_3od) δ 8.72 (dd, $J = 4.9, 1.6$ Hz, 1H), 7.68 (dd, $J = 7.8, 1.6$ Hz, 1H), 7.48 (dd, $J = 7.8, 4.9$ Hz, 1H), 7.38 (d, $J = 6.9$ Hz, 1H), 7.32 (s, 1H), 7.21 (dd, $J = 10.7, 8.5$ Hz, 1H), 6.76 – 6.57 (m, 1H), 6.30 (d, $J = 6.2$ Hz, 2H), 5.36 (t, $J = 7.6$ Hz, 1H), 4.96 (d, $J = 16.8$ Hz, 2H), 3.17 – 2.90 (m, 4H), 2.83 (dd, $J = 7.5, 4.4$ Hz, 2H).

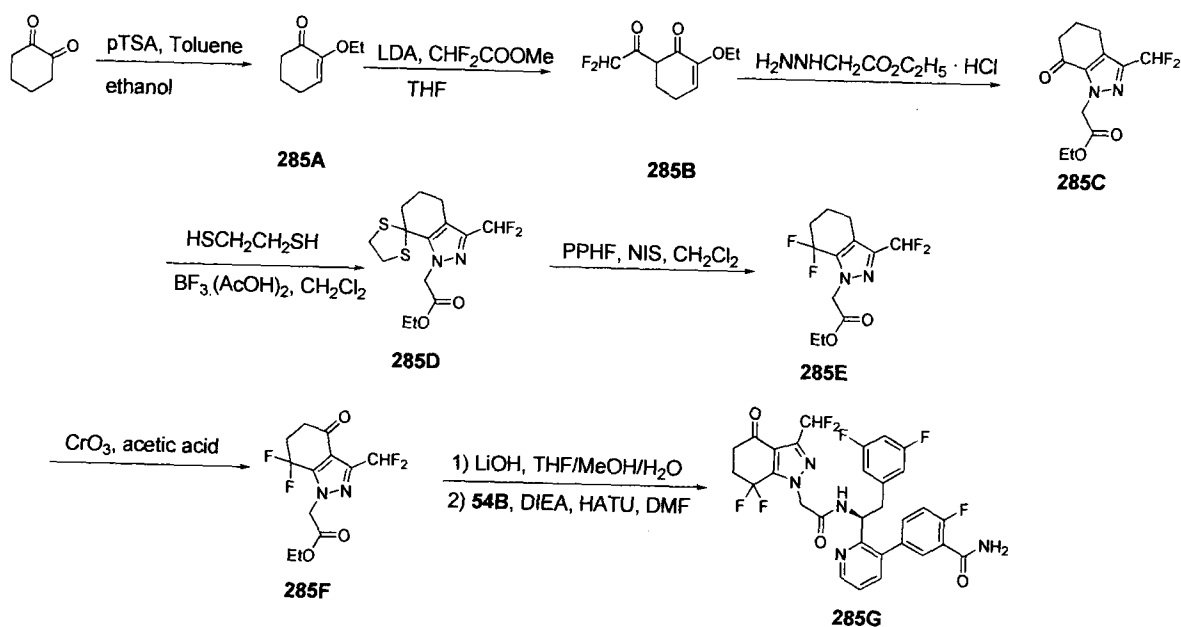
Example 284



Synthesis of (R)-N-(1-(5-(4-chlorophenyl)pyrimidin-4-yl)-2-(3,5-difluorophenyl)ethyl)-2-(5-hydroxy-1H-indol-3-yl)acetamide (**284**):

Compound 284 was prepared (21 mg) according to the method presented for the synthesis of Example 279G substituting 2-(5-hydroxy-1H-indol-3-yl)acetic acid for 2-(5,6-dimethyl-1H-benzo[d]imidazol-1-yl)acetic acid to afford the title compound: MS (m/z) 518.8 $[M+H]^+$. 1H NMR (400 MHz, cd_3od) δ 9.10 (s, 1H), 8.48 (s, 1H), 7.39 (d, $J = 8.3$ Hz, 2H), 7.15 (dd, $J = 17.6, 8.5$ Hz, 3H), 7.06 (s, 1H), 6.83 (d, $J = 2.1$ Hz, 1H), 6.68 (dd, $J = 12.7, 5.8$ Hz, 2H), 6.30 (d, $J = 6.5$ Hz, 2H), 5.40 (t, $J = 7.5$ Hz, 1H), 3.71 – 3.50 (m, 2H), 3.06 – 2.84 (m, 2H).

Example 285:



Synthesis of 2-ethoxycyclohex-2-enone (285A):

5 gram of cyclohexane-1,2-dione was dissolved in a mixture of 100 mL of toluene and 50 mL of ethanol. To it was added 1 gram of p-Toluenesulfonic acid and the solution was heated at reflux for one day; then cooled down and removed the solvent. The residue was dissolved in CH_2Cl_2 and washed with NaHCO_3 (sat'd aqueous solution) and half brine. The organic layer was separated, dried over MgSO_4 , filtered and concentrated. The residue was purified by silica gel chromatography eluting with EtOAc/Hexanes to afford 4.6 gram of the title compound. MS (m/z) 141.08 $[\text{M}+\text{H}]^+$.

Synthesis of 6-(2,2-difluoroacetyl)-2-ethoxycyclohex-2-enone (285B):

Compound 285B was prepared according to the method presented in the synthesis of Example 60B utilizing 2-ethoxycyclohex-2-enone to provide the title compound. MS (m/z) 219.12 $[\text{M}+\text{H}]^+$.

Synthesis of ethyl 2-(3-(difluoromethyl)-7-oxo-4,5,6,7-tetrahydro-1H-indazol-1-yl)acetate (285C):

Compound 285C was prepared according to the method presented in the synthesis of Example 60C utilizing 6-(2,2-difluoroacetyl)-2-ethoxycyclohex-2-enone to provide the title compound. MS (m/z) 273.11 $[\text{M}+\text{H}]^+$.

Synthesis of ethyl 2-(3'-(difluoromethyl)-5',6'-dihydrospiro[[1,3]dithiolane-2,7'-indazole]-1'-(4'H)-yl)acetate (**285D**):

Compound 285D was prepared according to the method presented in the synthesis of Example 283A utilizing ethyl 2-(3-(difluoromethyl)-7-oxo-4,5,6,7-tetrahydro-1H-indazol-1-yl)acetate to provide the title compound. MS (m/z) 349.28 $[M+H]^+$.

Synthesis of ethyl 2-(3-(difluoromethyl)-7,7-difluoro-4,5,6,7-tetrahydro-1H-indazol-1-yl)acetate (**285E**):

Compound 285E was prepared according to the method presented in the synthesis of Example 283B utilizing ethyl 2-(3'-(difluoromethyl)-5',6'-dihydrospiro[[1,3]dithiolane-2,7'-indazole]-1'-(4'H)-yl)acetate to provide the title compound. MS (m/z) 295.02 $[M+H]^+$.

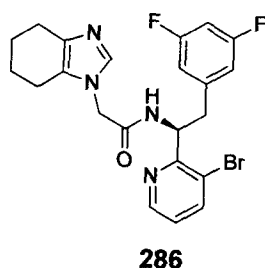
Synthesis of ethyl 2-(3-(difluoromethyl)-7,7-difluoro-4-oxo-4,5,6,7-tetrahydro-1H-indazol-1-yl)acetate (**285F**):

Compound 285F was prepared according to the method presented in the synthesis of Example 272A utilizing ethyl 2-(3-(difluoromethyl)-7,7-difluoro-4,5,6,7-tetrahydro-1H-indazol-1-yl)acetate to provide the title compound. MS (m/z) 309.01 $[M+H]^+$.

Synthesis of (S)-5-(2-(1-(2-(3-(difluoromethyl)-7,7-difluoro-4-oxo-4,5,6,7-tetrahydro-1H-indazol-1-yl)acetamido)-2-(3,5-difluorophenyl)ethyl)pyridin-3-yl)-2-fluorobenzamide (**285G**):

Compound 285G was prepared (6 mg) according to the method presented in the synthesis of Example 54 utilizing Compound 54B and ethyl 2-(3-(difluoromethyl)-7,7-difluoro-4-oxo-4,5,6,7-tetrahydro-1H-indazol-1-yl)acetic acid to provide the title compound; MS (m/z) 634.43 $[M+H]^+$. ^1H NMR (400 MHz, cd_3od) δ 8.72 (dd, $J = 4.9, 1.6$ Hz, 1H), 7.63 (dd, $J = 7.8, 1.6$ Hz, 1H), 7.44 (dd, $J = 7.8, 4.9$ Hz, 1H), 7.39 (d, $J = 7.0$ Hz, 1H), 7.29 (s, 1H), 7.20 (t, $J = 5.3$ Hz, 1H), 6.99 (t, $J = 53.5$ Hz, 1H), 6.66 (t, $J = 9.2$ Hz, 1H), 6.32 (d, $J = 6.2$ Hz, 2H), 5.36 (t, $J = 7.5$ Hz, 1H), 5.12 (s, 2H), 3.17 – 3.00 (m, 2H), 2.85 – 2.56 (m, 4H).

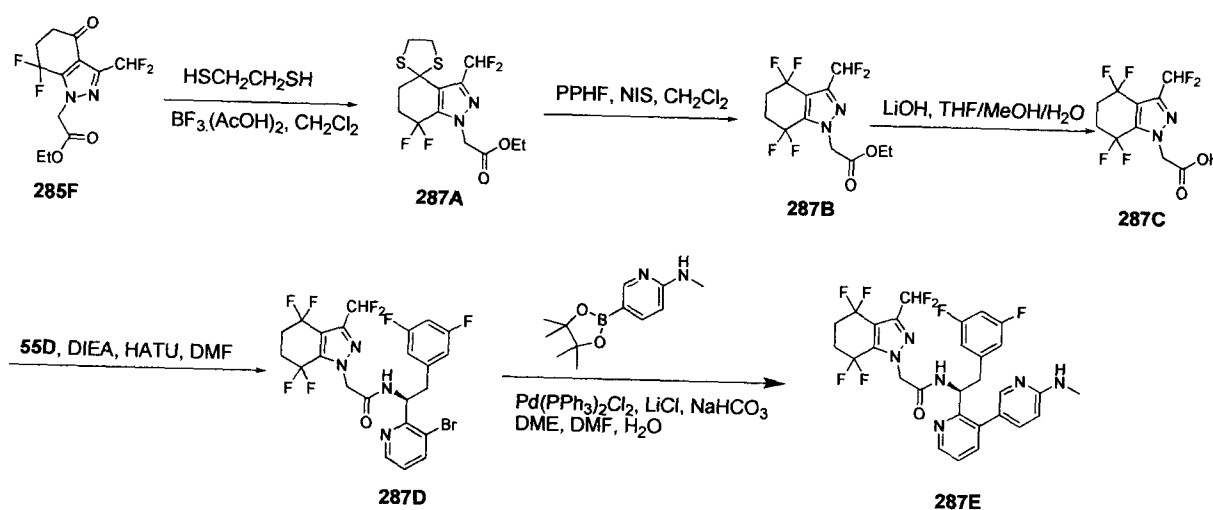
Example 286



Synthesis of (S)-N-(1-(3-bromopyridin-2-yl)-2-(3,5-difluorophenyl)ethyl)-2-(4,5,6,7-tetrahydro-1H-benzo[d]imidazol-1-yl)acetamide (**286**):

- 5 Compound **286** was prepared (8 mg) according to the method presented in the synthesis of Example 57 utilizing Compound **55D** and 2-(4,5,6,7-tetrahydro-1H-benzo[d]imidazol-1-yl)acetic acid to afford the title compound. MS (m/z) 475.1 $[M+H]^+$. 1H NMR (400 MHz, $cdCl_3$) δ 8.72 (s, 1H), 8.52 (s, 1H), 8.11 (m, 1H), 7.98 (d, $J = 8.0$ Hz, 1H), 6.73 – 6.54 (m, 3H), 5.78 (d, $J = 5.5$ Hz, 1H), 4.78 (d, $J = 22.5$ Hz, 2H), 3.18 (dd, $J = 13.6, 5.2$ Hz, 1H), 3.00 (dd, $J = 13.5,$
- 10 8.2 Hz, 1H), 2.66 (s, 2H), 2.42 (s, 2H), 1.84 (s, 4H).

Example 287



- 15 Synthesis of ethyl 2-(3'-(difluoromethyl)-7',7'-difluoro-6',7'-dihydrospiro[[1,3]dithiolane-2,4'-indazole]-1'(5'H)-yl)acetate (**287A**):

Compound **287A** was prepared according to the method presented in the synthesis of Example 283A utilizing ethyl 2-(3-(difluoromethyl)-7,7-difluoro-4-oxo-4,5,6,7-tetrahydro-1H-indazol-1-yl)acetate. MS (m/z) 385.26 $[M+H]^+$.

Synthesis of ethyl 2-(3-(difluoromethyl)-4,4,7,7-tetrafluoro-4,5,6,7-tetrahydro-1H-indazol-1-yl)acetate (**287B**):

Compound 287B was prepared according to the method presented in the synthesis of Example 283B utilizing ethyl 2-(3'-(difluoromethyl)-7',7'-difluoro-6',7'-dihydrospiro[[1,3]dithiolane-2,4'-indazole]-1'(5'H)-yl)acetate and substituting 2 mol equivalent of *N*-iodosuccinimide for 1,3-dibromo-5,5-dimethylhydantoin to afford the title compound. MS (m/z) 330.98 $[M+H]^+$.

Synthesis of 2-(3-(difluoromethyl)-4,4,7,7-tetrafluoro-4,5,6,7-tetrahydro-1H-indazol-1-yl)acetic acid (**287C**):

Compound 287C was prepared according to the method presented in the synthesis of Example 60G utilizing ethyl 2-(3-(difluoromethyl)-4,4,7,7-tetrafluoro-4,5,6,7-tetrahydro-1H-indazol-1-yl)acetate to afford the title compound. MS (m/z) 303.08 $[M+H]^+$.

Synthesis of (S)-N-(1-(3-bromopyridin-2-yl)-2-(3,5-difluorophenyl)ethyl)-2-(3-

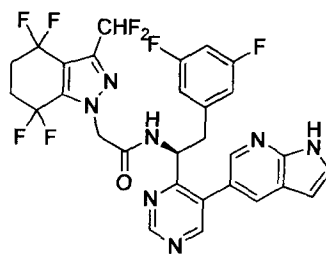
(difluoromethyl)-4,4,7,7-tetrafluoro-4,5,6,7-tetrahydro-1H-indazol-1-yl)acetamide (**287D**):

Compound 287D was prepared according to the method presented in the synthesis of Example 55E utilizing Compound 55D and 2-(3-(difluoromethyl)-4,4,7,7-tetrafluoro-4,5,6,7-tetrahydro-1H-indazol-1-yl)acetic acid to afford the title compound. MS (m/z) 597.88 $[M+H]^+$.

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-(6'-(methylamino)-3,3'-bipyridin-2-yl)ethyl)acetamide (**287E**):

Compound 287E was prepared (9 mg) according to the method presented in the synthesis of Example 61D substituting *N*-methyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridin-2-amine for 5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrrolo[2,3-*b*]pyridine to provide the title compound. MS (m/z) 625.22 $[M+H]^+$. ^1H NMR (400 MHz, cd_3od) δ 8.74 (dd, $J = 4.7$, 1.6 Hz, 1H), 7.64 – 7.53 (m, 2H), 7.47 (s, 1H), 7.39 (dd, $J = 7.8$, 4.8 Hz, 1H), 6.98 (d, $J = 9.2$ Hz, 1H), 6.92 – 6.62 (m, 2H), 6.42 (d, $J = 6.3$ Hz, 2H), 5.28 (t, $J = 7.6$ Hz, 1H), 5.13 – 4.96 (m, 2H), 3.13 (d, $J = 7.7$ Hz, 2H), 3.02 (s, 3H), 2.50 (d, $J = 12.1$ Hz, 4H).

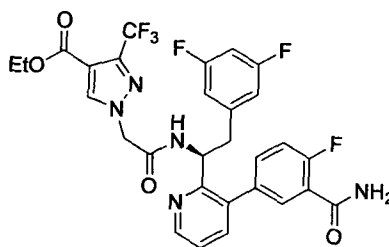
Example 288

**288**

Synthesis of (S)-N-(1-(5-(1H-pyrrolo[2,3-b]pyridin-5-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 (**288**):

Compound **288** was prepared (35 mg) according to the method presented in the synthesis of Example 13 utilizing Compound 172C and 2-(3-(difluoromethyl)-4,4,7,7-tetrafluoro-4,5,6,7-tetrahydro-1H-indazol-1-yl)acetic acid to provide the title compound. MS (m/z) 636.29 $[M+H]^+$. 1H NMR (400 MHz, cd_3od) δ 9.28 (s, 1H), 9.16 (d, $J = 7.8$ Hz, 1H), 8.62 (s, 1H), 8.10 (s, 1H), 7.98 (s, 1H), 7.60 (d, $J = 3.5$ Hz, 1H), 6.99 – 6.57 (m, 3H), 6.35 (d, $J = 6.1$ Hz, 2H), 5.47 – 5.25 (m, 1H), 5.06 (s, 2H), 3.12 (t, $J = 10.7$ Hz, 2H), 2.65 – 2.34 (m, 4H).

Example 289

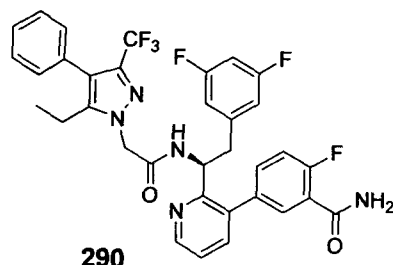
**289**

Synthesis of (S)-ethyl 1-(2-(1-(3-(3-carbamoyl-4-fluorophenyl)pyridin-2-yl)-2-(3,5-difluorophenyl)ethylamino)-2-oxoethyl)-3-(trifluoromethyl)-1H-pyrazole-4-carboxylate (**289**):

Compound **289** was prepared (10 mg) according to the method presented in the synthesis of Example 56B utilizing Compound 56A and ethyl 3-(trifluoromethyl)-1H-pyrazole-4-carboxylate to provide the title compound. MS (m/z) 620.21 $[M+H]^+$. 1H NMR (400 MHz, cd_3od) δ 8.68 (dd, $J = 4.8, 1.6$ Hz, 1H), 8.28 (s, 1H), 7.55 (dd, $J = 7.8, 1.6$ Hz, 1H), 7.45 – 7.34 (m, 2H), 7.31 (s, 1H), 7.20 (dd, $J = 10.8, 8.5$ Hz, 1H), 6.64 (m, 1H), 6.29 (d, $J = 6.2$ Hz, 2H), 5.33 (dd, $J = 8.6,$

6.5 Hz, 1H), 4.97 (s, 2H), 4.28 (q, $J = 7.1$ Hz, 2H), 3.06 (qd, $J = 12.9, 7.6$ Hz, 2H), 1.32 (t, $J = 7.1$ Hz, 3H).

Example 290

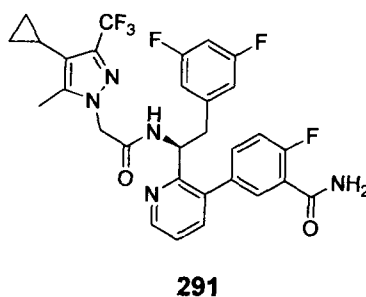


Synthesis of (S)-5-(2-(2-(3,5-difluorophenyl)-1-(2-(5-ethyl-4-phenyl-3-(trifluoromethyl)-1H-pyrazol-1-yl)acetamido)ethyl)pyridin-3-yl)-2-fluorobenzamide (**290**):

Compound 290 was prepared (4 mg) according to the method presented in the synthesis of

Example 276 substituting (S)-5-(2-(1-(2-(4-bromo-5-ethyl-3-(trifluoromethyl)-1H-pyrazol-1-yl)acetamido)-2-(3,5-difluorophenyl)ethyl)pyridin-3-yl)-2-fluorobenzamide (**58**) and phenylboronic acid for (S)-5-(2-(1-(2-(4-bromo-3-(trifluoromethyl)-1H-pyrazol-1-yl)acetamido)-2-(3,5-difluorophenyl)ethyl)pyridin-3-yl)-2-fluorobenzamide and cyclopropane boronic acid to provide the title compound. MS (m/z) 652.43 $[M+H]^+$. 1H NMR (400 MHz, cd_3od) δ 8.70 (dd, $J = 4.9, 1.6$ Hz, 1H), 7.64 (dd, $J = 7.8, 1.6$ Hz, 1H), 7.56 – 7.34 (m, 6H), 7.28 – 7.16 (m, 3H), 6.67 (t, $J = 9.3$ Hz, 1H), 6.35 (d, $J = 6.2$ Hz, 2H), 5.39 (t, $J = 7.5$ Hz, 1H), 4.95 (s, 2H), 3.08 (d, $J = 7.5$ Hz, 2H), 2.50 (dt, $J = 10.4, 7.6$ Hz, 2H), 0.94 (t, $J = 7.6$ Hz, 3H).

Example 291



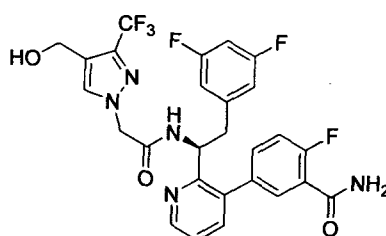
Synthesis of (S)-5-(2-(1-(2-(4-cyclopropyl-5-methyl-3-(trifluoromethyl)-1H-pyrazol-1-yl)acetamido)-2-(3,5-difluorophenyl)ethyl)pyridin-3-yl)-2-fluorobenzamide (**291**):

Compound 291 was prepared (25 mg) according to the method presented for the synthesis of Example 276 substituting (S)-5-(2-(1-(2-(4-bromo-5-methyl-3-(trifluoromethyl)-1H-pyrazol-1-yl)acetamido)-2-(3,5-difluorophenyl)ethyl)pyridin-3-yl)-2-fluorobenzamide (**275**) for (S)-5-(2-(1-(2-(4-bromo-3-(trifluoromethyl)-1H-pyrazol-1-yl)acetamido)-2-(3,5-

5 difluorophenyl)ethyl)pyridin-3-yl)-2-fluorobenzamide to provide the title compound: MS (m/z) 602.32 $[M+H]^+$. 1H NMR (400 MHz, cd_3od) δ 8.70 (dd, $J = 4.9, 1.6$ Hz, 1H), 7.68 (dd, $J = 7.8, 1.6$ Hz, 1H), 7.56 – 7.42 (m, 2H), 7.35 (s, 1H), 7.22 (dd, $J = 10.7, 8.5$ Hz, 1H), 6.79 – 6.60 (m, 1H), 6.33 (d, $J = 6.2$ Hz, 2H), 5.36 (t, $J = 7.6$ Hz, 1H), 4.83 (s, 2H), 3.05 (d, $J = 7.6$ Hz, 2H), 2.16 (s, 3H), 1.53 (m, 1H), 0.93 – 0.73 (m, 2H), 0.51 (q, $J = 5.7$ Hz, 2H).

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Example 292

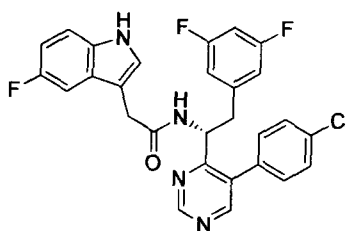
**292**

(S)-5-(2-(2-(3,5-difluorophenyl)-1-(2-(4-(hydroxymethyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl)acetamido)ethyl)pyridin-3-yl)-2-fluorobenzamide (**292**):

Compound 292 was prepared (10 mg) according to the method presented for the synthesis of Example 333 to afford the title compound as a side product. MS (m/z) 578.20 $[M+H]^+$. 1H NMR (400 MHz, cd_3od) δ 8.70 (dd, $J = 4.9, 1.6$ Hz, 1H), 7.71 (s, 1H), 7.63 (dd, $J = 7.8, 1.7$ Hz, 1H), 7.47 – 7.38 (m, 2H), 7.30 (s, 1H), 7.21 (dd, $J = 10.7, 8.5$ Hz, 1H), 6.73 – 6.55 (m, 1H), 6.30 (d, $J = 6.2$ Hz, 2H), 5.35 (dd, $J = 13.2, 6.4$ Hz, 1H), 4.92 (s, 2H), 4.55 (s, 2H), 3.15 – 2.94 (m, 2H).

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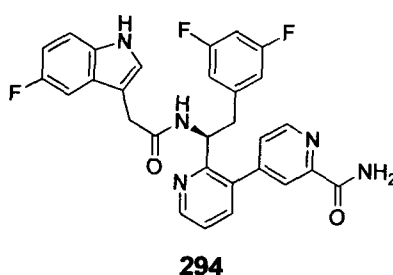
Example 293

**293**

Synthesis of (R)-N-(1-(5-(4-chlorophenyl)pyrimidin-4-yl)-2-(3,5-difluorophenyl)ethyl)-2-(5-fluoro-1H-indol-3-yl)acetamide (**293**):

Compound 293 was prepared (24 mg) according to the method presented for the synthesis of Example 279G substituting 2-(5-fluoro-1H-indol-3-yl)acetic acid for 2-(5,6-dimethyl-1H-benzo[d]imidazol-1-yl)acetic acid to afford the title compound: MS (m/z) 521.2 $[M+H]^+$. 1H NMR (400 MHz, $cdCl_3$) δ 9.04 (s, 1H), 8.55 (s, 1H), 8.24 (s, 1H), 7.46 (d, $J = 8.2$ Hz, 2H), 7.35 (dd, $J = 8.6, 4.2$ Hz, 1H), 7.19 (s, 1H), 7.12 (d, $J = 8.2$ Hz, 2H), 7.01 (t, $J = 9.2$ Hz, 2H), 6.82 (d, $J = 7.9$ Hz, 1H), 6.56 (t, $J = 8.8$ Hz, 1H), 6.07 (d, $J = 5.9$ Hz, 2H), 5.52 (q, $J = 7.5$ Hz, 1H), 3.81 – 3.61 (m, 2H), 2.83 – 2.65 (m, 2H).

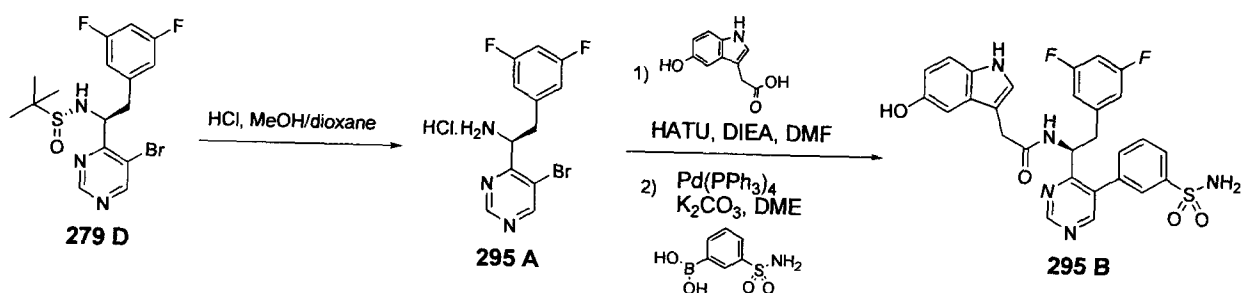
Example 294



Synthesis of (S)-2-(2-(3,5-difluorophenyl)-1-(2-(5-fluoro-1H-indol-3-yl)acetamido)ethyl)-3,4'-bipyridine-2'-carboxamide (**294**):

(S)-N-(1-(2'-cyano-3,4'-bipyridin-2-yl)-2-(3,5-difluorophenyl)ethyl)-2-(5-fluoro-1H-indol-3-yl)acetamide (**377**, 10 mg) was dissolved in 1 mL of THF and cooled down to 0 °C with ice-water bath. To it was added 0.05 mL of KOH solution (50 % in H_2O) and 0.1 mL of hydrogen peroxide solution [30 % (w/w) in water]. The reaction was allowed to warm to ambient temperature and stirred for 16 hours and then concentrated. The residue was purified by reverse phase HPLC eluting with acetonitrile/water (with 0.1% TFA) to afford 5.9 mg of the title compound. MS (m/z) 529.9 $[M+H]^+$. 1H NMR (400 MHz, $cdCl_3$) δ 8.68 (d, $J = 5.0$ Hz, 1H), 8.52 (d, $J = 4.5$ Hz, 1H), 8.19 – 8.09 (m, 2H), 7.97 (s, 1H), 7.86 (s, 1H), 7.80 (d, $J = 7.9$ Hz, 1H), 7.67 – 7.50 (m, 2H), 7.26 – 7.20 (m, 1H), 7.13 (s, 1H), 6.92 – 6.75 (m, 2H), 6.51 (m, 2H), 6.03 (d, $J = 5.8$ Hz, 2H), 5.28 (dd, $J = 15.9, 7.6$ Hz, 1H), 3.74 – 3.49 (m, 2H), 2.97 (dd, $J = 13.6, 7.2$ Hz, 1H), 2.87 – 2.78 (m, 1H).

Example 295



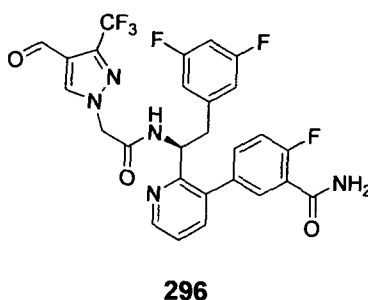
Synthesis of (S)-1-(5-bromopyrimidin-4-yl)-2-(3,5-difluorophenyl)ethanamine hydrochloride (**295A**):

- 5 Compound **295A** was prepared according to the method presented for the synthesis of Example 279F substituting Compound **279D** for Compound **279E** to afford the title compound: MS (m/z) 316.2 $[M+H]^+$.

Synthesis of (S)-N-(2-(3,5-difluorophenyl)-1-(5-(3-sulfamoylphenyl)pyrimidin-4-yl)ethyl)-2-(5-hydroxy-1H-indol-3-yl)acetamide (**295B**):

- 10 Compound **295B** was prepared (19 mg) according to the method presented in the synthesis of Example 57 utilizing Compound **295A** and 2-(5-hydroxy-1H-indol-3-yl)acetic acid, then Suzuki coupling with 3-sulfamoylphenylboronic acid to afford the title compound. MS (m/z) 564.2 $[M+H]^+$. 1H NMR (400 MHz, cd_3od) δ 9.05 (s, 1H), 8.45 (s, 1H), 7.87 (d, $J = 8.0$ Hz, 1H), 7.72 (s, 1H), 7.49 (t, $J = 7.8$ Hz, 1H), 7.27 (d, $J = 7.6$ Hz, 1H), 7.07 (d, $J = 8.7$ Hz, 1H), 6.96 (s, 1H), 6.73 (s, 1H), 6.57 (d, $J = 8.6$ Hz, 2H), 6.23 (d, $J = 6.8$ Hz, 2H), 5.29 (t, $J = 7.5$ Hz, 1H), 3.66 – 3.40 (m, 2H), 2.90 (d, $J = 7.5$ Hz, 2H).

Example 296

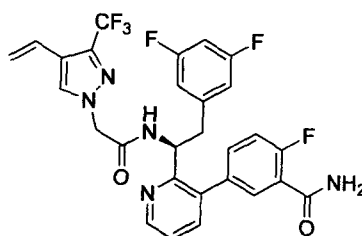


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Synthesis of (S)-5-(2-(2-(3,5-difluorophenyl)-1-(2-(4-formyl-3-(trifluoromethyl)-1H-pyrazol-1-yl)acetamido)ethyl)pyridin-3-yl)-2-fluorobenzamide (**296**):

Compound 296 was prepared (4 mg) according to the method presented in the synthesis of Example 56B utilizing compound 56A and 3-(trifluoromethyl)-1H-pyrazole-4-carbaldehyde to provide the title compound. MS (m/z) 620.21 $[M+H]^+$. 1H NMR (400 MHz, $cdCl_3$) δ 9.97 (s, 1H), 8.59 (d, $J = 3.3$ Hz, 1H), 8.14 (s, 1H), 7.64 (d, $J = 7.0$ Hz, 1H), 7.52 (d, $J = 7.9$ Hz, 1H), 7.48 – 7.37 (m, 1H), 7.33 (m, 1H), 7.22 – 7.09 (m, 2H), 6.73 (m, 1H), 6.56 (d, $J = 9.1$ Hz, 1H), 6.12 (d, $J = 6.6$ Hz, 2H), 5.87 (s, 1H), 5.44 (d, $J = 6.3$ Hz, 1H), 4.89 (s, 2H), 2.93 (s, 2H).

Example 297



297

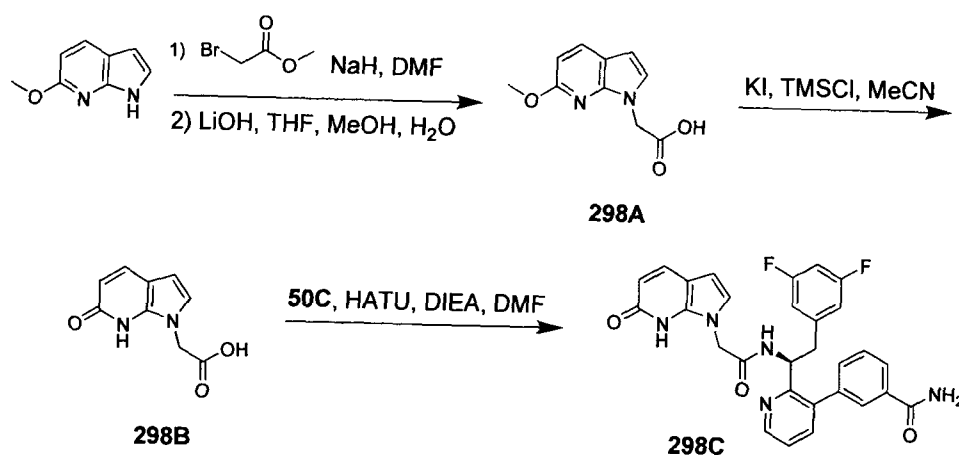
Synthesis of (S)-5-(2-(2-(3,5-difluorophenyl)-1-(2-(3-(trifluoromethyl)-4-vinyl-1H-pyrazol-1-yl)acetamido)ethyl)pyridin-3-yl)-2-fluorobenzamide (**297**):

(S)-5-(2-(2-(3,5-difluorophenyl)-1-(2-(4-ethynyl-3-(trifluoromethyl)-1H-pyrazol-1-yl)acetamido)ethyl)pyridin-3-yl)-2-fluorobenzamide (**341**, 40 mg) was dissolved in 10 mL of

EtOAc. The system was purged with argon and then 30 mg of Lindlar Catalyst was added. The reaction was stirred for 20 hours under 1 atm H_2 at ambient temperature. Upon completion of the reaction, it was filtered through a pad of celite and washed with EtOAc. The filtrate was collected and the volatiles were removed in vacuo. The residue was purified by reverse phase HPLC eluting with acetonitrile/water (with 0.1% TFA) to afford 15 mg of the title compound.

MS (m/z) 574.40 $[M+H]^+$. 1H NMR (400 MHz, cd_3od) δ 8.69 (dd, $J = 4.9, 1.6$ Hz, 1H), 7.93 (s, 1H), 7.64 (dd, $J = 7.8, 1.6$ Hz, 1H), 7.49 – 7.40 (m, 2H), 7.33 (s, 1H), 7.21 (dd, $J = 10.7, 8.6$ Hz, 1H), 6.65 (t, $J = 9.2$ Hz, 1H), 6.60 – 6.48 (m, 1H), 6.30 (d, $J = 6.2$ Hz, 2H), 5.58 (d, $J = 17.7$ Hz, 1H), 5.35 (t, $J = 7.5$ Hz, 1H), 5.22 (dd, $J = 11.2, 1.2$ Hz, 1H), 4.91 (s, 2H), 3.06 (d, $J = 7.8$ Hz, 2H).

Example 298



Synthesis of 2-(6-methoxy-1H-pyrrolo[2,3-b]pyridin-1-yl)acetic acid (**298A**):

6-methoxy-1H-pyrrolo[2,3-b]pyridine (250 mg, 1.69 mmol) was dissolved in 2 mL of DMF and cooled down to 0 °C. To it was added NaH (60% in oil dispersion, 68 mg, 1.69 mmol) portionwise. The mixture was stirred at ambient temperature for 20 min, a solution of methyl 2-bromoacetate (192 µL, 2 mmol) in 0.5 mL of DMF was added dropwise. It was stirred for 2 hours and quenched with saturated aqueous NH₄Cl solution. The mixture was partitioned between EtOAc and water. The organic layer was separated, dried over MgSO₄, filtered and concentrated to afford crude methyl 2-(6-methoxy-1H-pyrrolo[2,3-b]pyridin-1-yl)acetate which was dissolved in 5 mL of THF/MeOH/H₂O (3/2/1) and to it was added LiOH·H₂O (355 mg, 8.45 mmol). The mixture was stirred at ambient temperature for 20 min and concentrated to small volume. It was filtered and purified by reverse phase HPLC eluting with acetonitrile/water (with 0.1% TFA) to afford 186 mg of the title compound. MS (m/z) 205.1 [M-H]⁻

Synthesis of 2-(6-oxo-6,7-dihydro-1H-pyrrolo[2,3-b]pyridin-1-yl)acetic acid (**298B**):

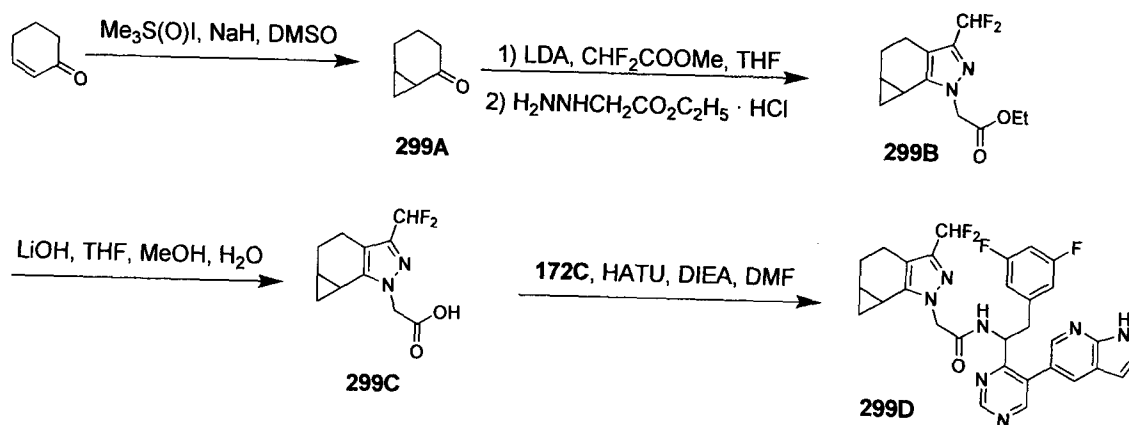
2-(6-methoxy-1H-pyrrolo[2,3-b]pyridin-1-yl)acetic acid (100 mg, 0.48 mmol) was dissolved in 5 mL of acetonitrile. To it was added KI (161 mg, 0.96 mmol) and TMSCl (122 µL, 0.96 mmol). The reaction mixture was heated up to 80 °C for 4 hours and cooled down to ambient temperature. It was filtered and purified by reverse phase HPLC eluting with acetonitrile/water (with 0.1% TFA) to afford 30 mg of the title compound. MS (m/z) 193.3 [M+H]⁺.

Synthesis of (S)-3-(2-(2-(3,5-difluorophenyl)-1-(2-(6-oxo-6,7-dihydro-1H-pyrrolo[2,3-b]pyridin-1-yl)acetamido)ethyl)pyridin-3-yl)benzamide (**298C**):

Compound 298C was prepared (6 mg) according to the method presented in the synthesis of Example 50D utilizing compound 50C and 2-(6-oxo-6,7-dihydro-1H-pyrrolo[2,3-b]pyridin-1-

yl)acetic acid to provide the title compound. MS (m/z) 528.0 $[M+H]^+$. 1H NMR (400 MHz, cd_3od) δ 8.69 (d, $J = 4.9$ Hz, 1H), 7.95 (d, $J = 8.6$ Hz, 1H), 7.89 (d, $J = 7.8$ Hz, 1H), 7.70 (d, $J = 7.8$ Hz, 1H), 7.64 (s, 1H), 7.48 (dd, $J = 10.2, 5.0$ Hz, 2H), 7.28 (d, $J = 7.1$ Hz, 1H), 7.03 (d, $J = 3.5$ Hz, 1H), 6.64 (t, $J = 9.2$ Hz, 1H), 6.51 (d, $J = 8.5$ Hz, 1H), 6.46 (d, $J = 3.5$ Hz, 1H), 6.23 (d, $J = 6.2$ Hz, 2H), 5.42 (t, $J = 7.5$ Hz, 1H), 4.93 (s, 2H), 3.10 – 2.96 (m, 2H).

Example 299



10 Synthesis of bicyclo[4.1.0]heptan-2-one (**299A**):

Compound 299A was prepared according to the method presented in Tetrahedron, Vol. 51. No. 43, p. 11757, 1995.

1H NMR (400 MHz, $cdcl_3$) δ 2.27 – 2.18 (m, 1H), 2.05 – 1.79 (m, 4H), 1.72 – 1.47 (m, 3H), 1.14 (m, 1H), 1.08 – 0.92 (m, 1H).

15

Synthesis of ethyl 2-(3-(difluoromethyl)-5,5a,6,6a-tetrahydrocyclopropa[g]indazol-1(4H)-yl)acetate (**299B**):

Compound 299B was prepared according to the method presented in the synthesis of Example 60C utilizing bicyclo[4.1.0]heptan-2-one to provide the title compound as a mixture of

20

Synthesis of 2-(3-(difluoromethyl)-5,5a,6,6a-tetrahydrocyclopropa[g]indazol-1(4H)-yl)acetic acid (**299C**):

Ethyl 2-(3-(difluoromethyl)-5,5a,6,6a-tetrahydrocyclopropa[g]indazol-1(4H)-yl)acetate (27 mg, 0.1 mmol) was dissolved in 2 mL of THF/MeOH/ H_2O (3/2/1) and to it was added $LiOH \cdot H_2O$ (13 mg, 0.3 mmol). The mixture was stirred at ambient temperature for 10 min and cooled down

25

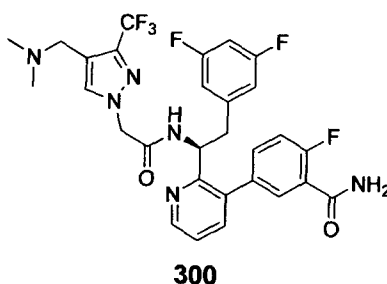
to 0 °C. It was acidified with 1N HCl and extracted with EtOAc. The organic layer was separated, dried over MgSO₄, filtered and concentrated to afford the title compound. MS (*m/z*) 243.12 [M+H]⁺.

5 Synthesis of N-(1-(5-(1H-pyrrolo[2,3-b]pyridin-5-yl)pyrimidin-4-yl)-2-(3,5-difluorophenyl)ethyl)-2-(3-(difluoromethyl)-5,5a,6,6a-tetrahydrocyclopropa[g]indazol-1(4H)-yl)acetamide (**299D**):

Compound 299D was prepared (30 mg) according to the method presented in the synthesis of Example 13 utilizing Compound 172C and 2-(3-(difluoromethyl)-5,5a,6,6a-

10 tetrahydrocyclopropa[g]indazol-1(4H)-yl)acetic acid to provide the title compound as mixture of diastereomers. MS (*m/z*) 576.38 [M+H]⁺. ¹H NMR (400 MHz, cd₃od) δ 9.20 (d, *J* = 2.1 Hz, 1H), 8.60 (s, 1H), 7.95 (s, 1H), 7.81 (d, *J* = 1.9 Hz, 1H), 7.46 (d, *J* = 3.5 Hz, 1H), 6.76 – 6.66 (m, 1H), 6.60 – 6.41 (m, 2H), 6.31 (t, *J* = 5.7 Hz, 2H), 5.48 (td, *J* = 7.5, 3.3 Hz, 1H), 4.87 (s, 2H), 3.12 – 2.94 (m, 2H), 2.70 (dd, *J* = 15.7, 5.7 Hz, 1H), 2.11 (ddt, *J* = 41.1, 27.6, 14.0 Hz, 2H),
15 1.88 – 1.69 (m, 2H), 1.60 (m, 1H), 0.94 (dtd, *J* = 13.2, 8.2, 4.9 Hz, 1H), 0.65 (m, 1H).

Example 300



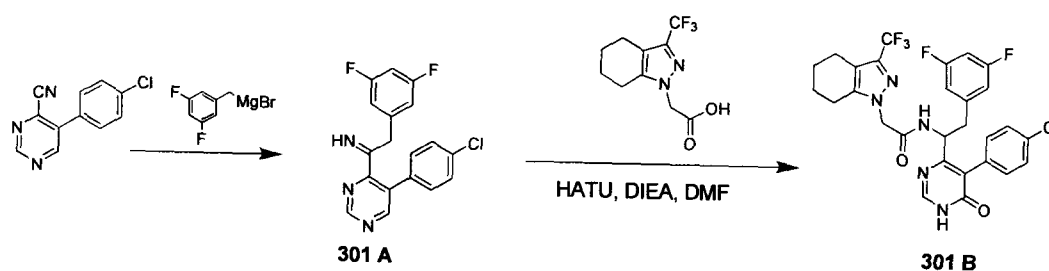
20

Synthesis of (S)-5-(2-(2-(3,5-difluorophenyl)-1-(2-(4-((dimethylamino)methyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl)acetamido)ethyl)pyridin-3-yl)-2-fluorobenzamide (**300**):

Compound 300 was prepared (8 mg) according to the method presented for the synthesis of Example 333 substituting dimethylamine hydrochloride for methylamine hydrochloride to afford

25 the title compound: MS (*m/z*) 605.29 [M+H]⁺. ¹H NMR (400 MHz, cd₃od) δ 8.70 (dd, *J* = 4.8, 1.6 Hz, 1H), 8.02 (s, 1H), 7.59 (dd, *J* = 7.8, 1.6 Hz, 1H), 7.49 (d, *J* = 5.0 Hz, 1H), 7.41 (dd, *J* = 7.8, 4.8 Hz, 1H), 7.31 – 7.14 (m, 2H), 6.66 (m, 1H), 6.33 (d, *J* = 6.2 Hz, 2H), 5.41 – 5.26 (m, 1H), 5.02 (s, 2H), 4.31 (s, 2H), 3.09 (qd, *J* = 13.0, 7.6 Hz, 2H), 2.86 (s, 6H).

Example 301



- 5 Synthesis of 1-(5-(4-chlorophenyl)pyrimidin-4-yl)-2-(3,5-difluorophenyl)ethanimine (**301A**):
 5-(4-chlorophenyl)pyrimidine-4-carbonitrile (215 mg, 1 mmol) was dissolved in toluene and
 cooled down to 0 °C. To it was added (3,5-difluorobenzyl)magnesium bromide (0.25 M in ether,
 4.8 ml, 1.2 mmol) dropwise. After stirring for 30 min the reaction was allowed to warm to
 ambient temperature and stirred for 1 hour. It was cooled down to 0 °C again and 3 mL of 2-
 10 butanol was added followed by NaBH₄ (76 mg, 2 mmol) and the reaction was stirred at ambient
 temperature for 16 hours. The reaction was quenched with water at 0 °C and extracted with
 EtOAc. The organic layer was separated, dried over MgSO₄, filtered and concentrated. The
 residue was purified by silica gel chromatography eluting with EtOAc/Hexanes to afford 100 mg
 of the title compound. MS (m/z) 344.2 [M+H]⁺.

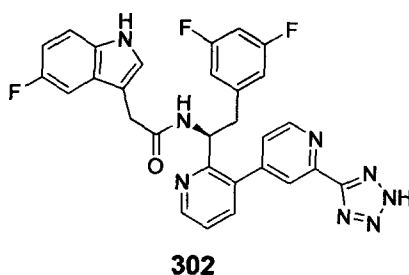
15

Synthesis of (S)-N-(1-(5-(4-chlorophenyl)-6-oxo-1,6-dihydropyrimidin-4-yl)-2-(3,5-
 difluorophenyl)ethyl)-2-(3-(trifluoromethyl)-4,5,6,7-tetrahydro-1H-indazol-1-yl)acetamide
 (**301B**):

- 2-(3-(trifluoromethyl)-4,5,6,7-tetrahydro-1H-indazol-1-yl)acetic acid (25 mg, 0.1 mmol) and 1-
 20 (5-(4-chlorophenyl)pyrimidin-4-yl)-2-(3,5-difluorophenyl)ethanimine (35 mg, 0.1 mmol) was
 dissolved in 1 mL of DMF and cooled down to 0 °C. To it was added *N,N*-
 Diisopropylethylamine (52 µL, 0.3 mmol) followed by HATU (46 mg, 0.12 mmol). The
 reaction was allowed to stir at 0 °C for 20 min and then purified by reverse phase HPLC eluting
 with acetonitrile/water (with 0.1% TFA). The fractions were combined and heated up to 60 °C
 25 for 20 min. After cooled down to room temperature it was purified by reverse phase HPLC again
 eluting with acetonitrile/water (with 0.1% TFA) to afford 5 mg of the title compound. MS (m/z)
 592.1 [M+H]⁺. ¹H NMR (400 MHz, cdcl₃) δ 9.54 (s, 1H), 8.41 (s, 1H), 7.49 – 7.34 (m, 3H), 7.11
 (t, *J* = 8.8 Hz, 2H), 6.68 (t, *J* = 8.8 Hz, 1H), 6.44 (d, *J* = 5.6 Hz, 2H), 4.99 (m, 1H), 4.68 (q, *J* =
 16.8 Hz, 2H), 2.79 – 2.50 (m, 4H), 2.47 – 2.23 (m, 2H), 1.97 – 1.70 (m, 4H).

30

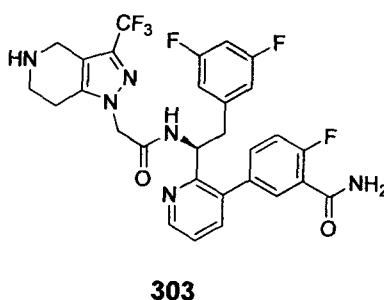
Example 302



Synthesis of (S)-N-(1-(2'-(2H-tetrazol-5-yl)-3,4'-bipyridin-2-yl)-2-(3,5-difluorophenyl)ethyl)-2-(5-fluoro-1H-indol-3-yl)acetamide (**302**):

(S)-N-(1-(2'-cyano-3,4'-bipyridin-2-yl)-2-(3,5-difluorophenyl)ethyl)-2-(5-fluoro-1H-indol-3-yl)acetamide (**377**, 8 mg, 0.016 mmol) was dissolved in 1 mL of isopropanol and 1 mL of water. To it was added zinc bromide (3.5 mg, 0.016 mmol) and sodium azide (3 mg, 0.048 mmol). The reaction mixture was heated up to 100 °C for 16 hours. It was cooled down and filtered. The residue was purified by reverse phase HPLC twice eluting with acetonitrile/water (with 0.1% TFA) to afford 3.5 mg of the title compound. MS (m/z) 555.2 [M+H]⁺. ¹H NMR (400 MHz, cd₃od) δ 8.61 (d, J = 4.4 Hz, 2H), 7.62 (s, 1H), 7.55 (d, J = 6.2 Hz, 1H), 7.41 – 7.28 (m, 2H), 7.19 (dd, J = 8.8, 4.4 Hz, 1H), 7.09 (s, 1H), 7.01 (d, J = 2.3 Hz, 1H), 6.79 – 6.69 (m, 1H), 6.43 (t, J = 9.2 Hz, 1H), 6.18 (d, J = 6.2 Hz, 2H), 5.27 (t, J = 7.6 Hz, 1H), 3.54 (s, 2H), 2.94 (d, J = 7.6 Hz, 2H).

Example 303

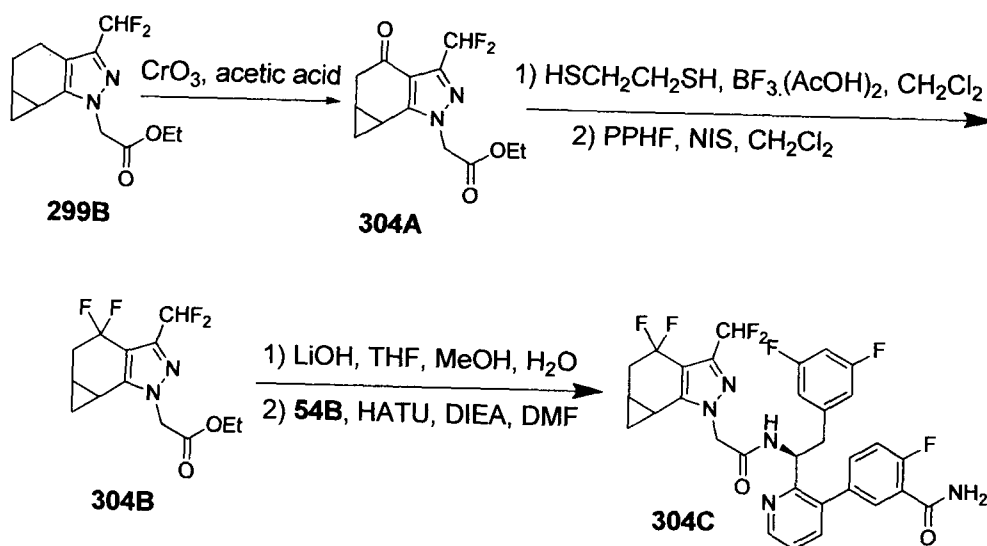


Synthesis of (S)-5-(2-(2-(3,5-difluorophenyl)-1-(2-(3-(trifluoromethyl)-4,5,6,7-tetrahydro-1H-pyrazolo[4,3-c]pyridin-1-yl)acetamido)ethyl)pyridin-3-yl)-2-fluorobenzamide (**303**):

(S)-tert-butyl 1-(2-(1-(3-(3-carbamoyl-4-fluorophenyl)pyridin-2-yl)-2-(3,5-difluorophenyl)ethylamino)-2-oxoethyl)-3-(trifluoromethyl)-6,7-dihydro-1H-pyrazolo[4,3-c]pyridine-5(4H)-carboxylate (**274**, 269 mg, 0.38 mmol) was dissolved in 3 mL of 1,4-dioxane

and to it was added 1 mL of HCl solution (4 N in 1,4-dioxane). The mixture was allowed to stir at ambient temperature for 1 day. To it was added diethyl ether and the resulting precipitate was collected by vacuum filtration and further high vacuum drying to afford 210 mg of the title compound. MS (m/z) 603.30 [M+H]⁺. ¹H NMR (400 MHz, cd₃od) δ 8.82 (dd, *J* = 5.4, 1.5 Hz, 1H), 8.03 (d, *J* = 7.9 Hz, 1H), 7.77 (dd, *J* = 7.9, 5.4 Hz, 1H), 7.67 (m, 1H), 7.32 (s, 1H), 7.28 – 7.19 (m, 1H), 6.73 (t, *J* = 9.2 Hz, 1H), 6.38 (d, *J* = 6.2 Hz, 2H), 5.41 (dd, *J* = 9.0, 6.5 Hz, 1H), 5.11 – 4.94 (m, 2H), 3.59 – 3.49 (m, 2H), 3.23 (dd, *J* = 13.3, 6.5 Hz, 1H), 3.12 – 3.06 (m, 1H), 3.02 (d, *J* = 5.8 Hz, 2H).

10 Example 304



Synthesis of ethyl 2-(3-(difluoromethyl)-4-oxo-5,5a,6,6a-tetrahydrocyclopropa[g]indazol-1(4H)-yl)acetate (**304A**):

Compound 304A was prepared according to the method presented in the synthesis of Example 272A substituting Compound 299B for ethyl 2-(3-(trifluoromethyl)-4,5,6,7-tetrahydro-1H-indazol-1-yl)acetate to afford the title compound; MS (m/z) 303.16 [M+H]⁺.

Synthesis of ethyl 2-(3-(difluoromethyl)-4,4-difluoro-5,5a,6,6a-tetrahydrocyclopropa[g]indazol-1(4H)-yl)acetate (**304B**):

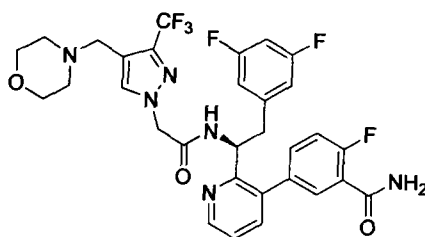
Compound 304B was prepared according to the method presented in the synthesis of Example 285E substituting Compound 304A for Compound 285C to afford the title compound. MS (m/z) 307.19 [M+H]⁺.

Synthesis of 5-(2-((1S)-1-(2-(3-(difluoromethyl)-4,4-difluoro-5,5a,6,6a-tetrahydrocyclopropa[g]indazol-1(4H)-yl)acetamido)-2-(3,5-difluorophenyl)ethyl)pyridin-3-yl)-2-fluorobenzamide (**304C**):

- 5 Compound 304C was prepared according to the method presented in the synthesis of Example 54 utilizing Compound 54B and 2-(4,4-difluoro-3-(trifluoromethyl)-5,5a,6,6a-tetrahydrocyclopropa[g]indazol-1(4H)-yl)acetic acid to provide 6 mg of the title compound. MS (m/z) 632.09 $[M+H]^+$. 1H NMR (400 MHz, cd_3od) δ 8.69 (t, $J = 3.3$ Hz, 1H), 7.68 – 7.55 (m, 1H), 7.51 – 7.40 (m, 2H), 7.31 (m, 1H), 7.22 (t, $J = 9.6$ Hz, 1H), 6.90 – 6.45 (m, 2H), 6.34 (dd, $J = 13.1, 6.4$ Hz, 2H), 5.36 (q, $J = 7.6$ Hz, 1H), 5.06 – 4.91 (m, 2H), 3.17 – 2.92 (m, 2H), 2.62 (t, $J = 16.4$ Hz, 1H), 2.39 – 2.17 (m, 1H), 2.04 (m, 1H), 1.77 (m, 1H), 1.17 (dd, $J = 14.2, 5.7$ Hz, 1H), 0.46 (m, 1H).

Example 305

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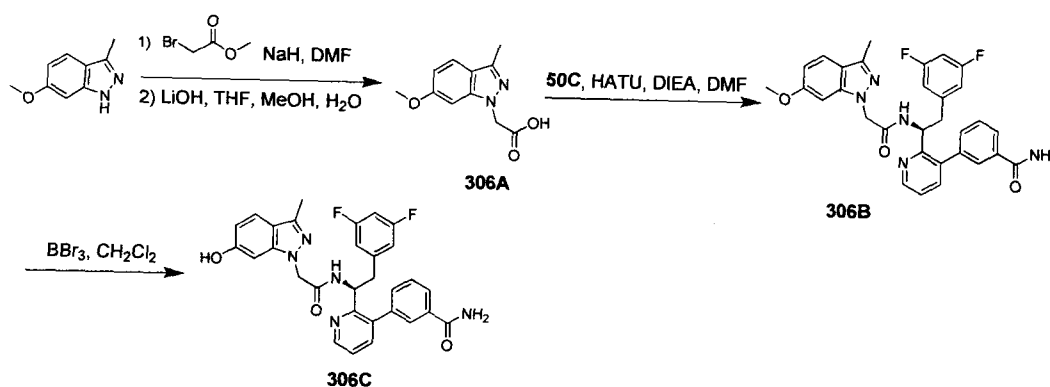
305

Synthesis of (S)-5-(2-(2-(3,5-difluorophenyl)-1-(2-(4-(morpholinomethyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl)acetamido)ethyl)pyridin-3-yl)-2-fluorobenzamide (**305**):

- 20 Compound 305 was prepared according to the method presented for the synthesis of Example 333 substituting morpholine for methylamine hydrochloride to afford 7 mg of the title compound: MS (m/z) 647.27 $[M+H]^+$. 1H NMR (400 MHz, cd_3od) δ 8.70 (dd, $J = 4.8, 1.6$ Hz, 1H), 8.02 (s, 1H), 7.68 – 7.58 (m, 1H), 7.52 (d, $J = 6.8$ Hz, 1H), 7.41 (dd, $J = 7.8, 4.8$ Hz, 1H), 7.30 – 7.10 (m, 2H), 6.66 (dd, $J = 10.4, 8.1$ Hz, 1H), 6.34 (d, $J = 6.2$ Hz, 2H), 5.38 – 5.28 (m, 1H), 5.02 (s, 2H), 4.35 (s, 2H), 4.04 (bs, 2H), 3.73 (bs, 2H), 3.40 (bs, 2H), 3.09 (m, 4H).

25

Example 306



Synthesis of 2-(6-methoxy-3-methyl-1H-indazol-1-yl)acetic acid (**306A**):

- Compound 306A was prepared according to the method presented for the synthesis of Example 298A substituting 6-methoxy-3-methyl-1H-indazole for 6-methoxy-1H-pyrrolo[2,3-b]pyridine to afford the title compound: MS (m/z) 221.3 $[\text{M}+\text{H}]^+$.

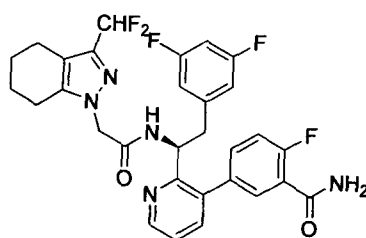
Synthesis of (S)-3-(2-(2-(3,5-difluorophenyl)-1-(2-(6-methoxy-3-methyl-1H-indazol-1-yl)acetamido)ethyl)pyridin-3-yl)benzamide (**306B**):

- Compound 306B was prepared according to the method presented in the synthesis of Example 50D utilizing Compound 50C and 2-(6-methoxy-3-methyl-1H-indazol-1-yl)acetic acid to provide the title compound. MS (m/z) 556.2 $[\text{M}+\text{H}]^+$.

Synthesis of (S)-3-(2-(2-(3,5-difluorophenyl)-1-(2-(6-hydroxy-3-methyl-1H-indazol-1-yl)acetamido)ethyl)pyridin-3-yl)benzamide (**306C**):

- (S)-3-(2-(2-(3,5-difluorophenyl)-1-(2-(6-methoxy-3-methyl-1H-indazol-1-yl)acetamido)ethyl)pyridin-3-yl)benzamide (21 mg, 0.038 mmol) was dissolved in 1 mL of CH_2Cl_2 and cooled down to -78°C with dry ice-acetone bath. To it was added BBr_3 (1 M in CH_2Cl_2) and the reaction mixture was allowed to warm to ambient temperature and stirred for 16 hours. It was quenched with NaHCO_3 (sat'd aqueous solution) and extracted with EtOAc. 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 9.3 mg of the title compound. MS (m/z) 542.0 $[\text{M}+\text{H}]^+$. ^1H NMR (400 MHz, cd_3od) δ 8.56 (d, $J = 4.9$ Hz, 1H), 7.79 (d, $J = 7.7$ Hz, 1H), 7.58 (d, $J = 7.7$ Hz, 1H), 7.49 (s, 1H), 7.46 – 7.32 (m, 3H), 7.16 (d, $J = 7.2$ Hz, 1H), 6.62 (d, $J = 8.8$ Hz, 1H), 6.56 (d, $J = 10.1$ Hz, 2H), 6.12 (d, $J = 6.5$ Hz, 2H), 5.35 (t, $J = 7.5$ Hz, 1H), 4.83 (s, 2H), 2.88 (d, $J = 7.6$ Hz, 2H), 2.39 (s, 3H).

Example 307

**307**

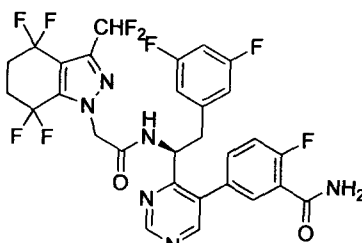
- 5 Synthesis of (S)-5-(2-(1-(2-(3-(difluoromethyl)-4,5,6,7-tetrahydro-1H-indazol-1-yl)acetamido)-2-(3,5-difluorophenyl)ethyl)pyridin-3-yl)-2-fluorobenzamide (**307**):

Compound 307 was prepared according to the method presented in the synthesis of Example 56B utilizing Compound 56A and 3-(difluoromethyl)-4,5,6,7-tetrahydro-1H-indazole to provide 6 mg of the title compound. MS (*m/z*) 584.36 [*M*+*H*]⁺.

- 10 ¹H NMR (400 MHz, *cdCl*₃) δ 9.59 – 9.33 (m, 3H), 8.79 (dd, *J* = 5.5, 1.4 Hz, 1H), 7.97 (dd, *J* = 7.9, 1.5 Hz, 1H), 7.82 – 7.58 (m, 2H), 7.34 – 7.26 (m, 1H), 6.99 (d, *J* = 9.8 Hz, 1H), 6.76 (m, 1H), 6.67 – 6.53 (m, 1H), 6.19 (d, *J* = 5.7 Hz, 2H), 5.47 (dd, *J* = 16.1, 7.2 Hz, 1H), 4.84 – 4.57 (m, 2H), 3.17 (dd, *J* = 13.6, 7.1 Hz, 1H), 3.01 (dd, *J* = 13.6, 9.1 Hz, 1H), 2.59 (t, *J* = 5.6 Hz, 2H), 2.42 (t, *J* = 10.4 Hz, 2H), 1.75 (dd, *J* = 30.7, 5.7 Hz, 4H).

15

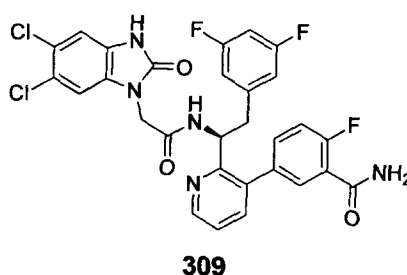
Example 308

**308**

- 20 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)pyrimidin-5-yl)-2-fluorobenzamide (**308**):
- Compound 308 was prepared according to the method presented in the synthesis of Example 54G utilizing Compound 136C and 2-(3-(difluoromethyl)-4,4,7,7-tetrafluoro-4,5,6,7-tetrahydro-1H-indazol-1-yl)acetic acid to provide 11 mg of the title compound. MS (*m/z*) 636.29 [*M*+*H*]⁺.

^1H NMR (400 MHz, cd_3od) δ 9.23 (s, 1H), 9.12 (d, $J = 7.9$ Hz, 1H), 8.55 (s, 1H), 7.46 (d, $J = 5.8$ Hz, 2H), 7.33 – 7.20 (m, 1H), 6.96 – 6.58 (m, 2H), 6.40 (d, $J = 6.1$ Hz, 2H), 5.36 (q, $J = 7.7$ Hz, 1H), 5.04 (s, 2H), 3.08 (d, $J = 7.6$ Hz, 2H), 2.63 – 2.33 (m, 4H).

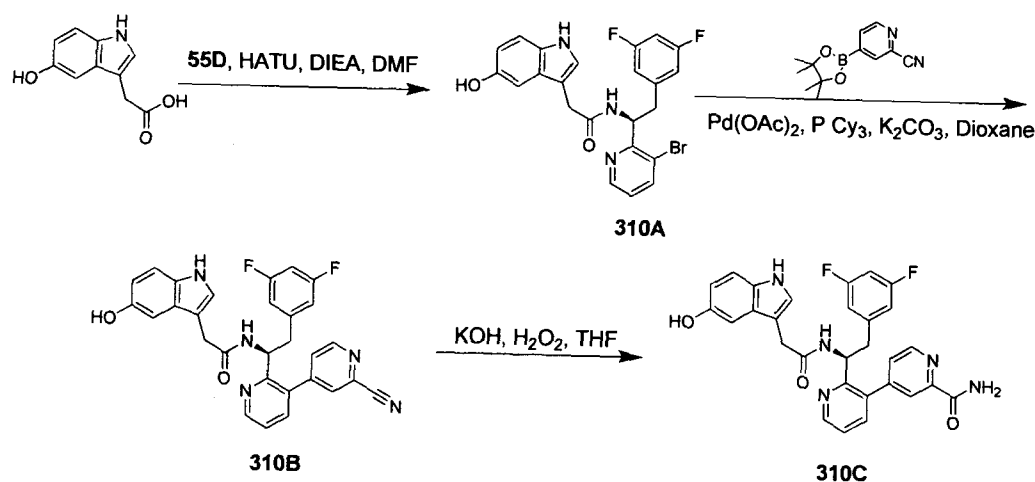
5 Example 309



Synthesis of (S)-5-(2-(1-(2-(5,6-dichloro-2-oxo-2,3-dihydro-1H-benzo[d]imidazol-1-yl)acetamido)-2-(3,5-difluorophenyl)ethyl)pyridin-3-yl)-2-fluorobenzamide (**309**):

- 10 Compound **309** was prepared according to the method presented in the synthesis of Example 56B utilizing Compound **56A** and 5,6-dichloro-1H-benzo[d]imidazol-2(3H)-one to provide 25 mg of the title compound. MS (m/z) 614.72 $[\text{M}+\text{H}]^+$. ^1H NMR (400 MHz, cd_3od) δ 8.72 (d, $J = 4.7$ Hz, 1H), 7.65 (d, $J = 7.7$ Hz, 1H), 7.53 – 7.30 (m, 3H), 7.27 – 7.14 (m, 2H), 7.07 (s, 1H), 6.66 (t, $J = 9.2$ Hz, 1H), 6.32 (d, $J = 6.2$ Hz, 2H), 5.36 (t, $J = 7.7$ Hz, 1H), 4.64 – 4.44 (m, 2H),
- 15 3.07 (d, $J = 7.4$ Hz, 2H).

Example 310



- 20 Synthesis of (S)-N-(1-(3-bromopyridin-2-yl)-2-(3,5-difluorophenyl)ethyl)-2-(5-hydroxy-1H-indol-3-yl)acetamide (**310A**):

Compound 310A was prepared according to the method presented in the synthesis of Example 55E utilizing compound **55D** and 2-(5-hydroxy-1H-indol-3-yl)acetic acid to provide the title compound. MS (m/z) 486.00 $[M+H]^+$.

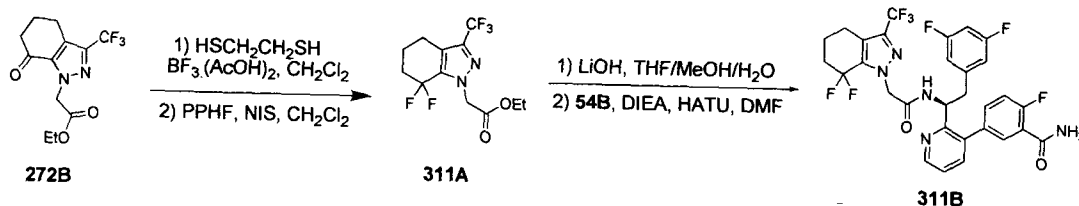
5 Synthesis of (S)-N-(1-(2'-cyano-3,4'-bipyridin-2-yl)-2-(3,5-difluorophenyl)ethyl)-2-(5-hydroxy-1H-indol-3-yl)acetamide (**310B**):

To a mixture of Compound 310A (49 mg, 0.1 mmol), 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)picolinonitrile (35 mg, 0.15 mmol) and potassium carbonate (41 mg, 0.3 mmol) was added 1 mL of 1,4-dioxane. After the system was purged with argon, palladium (II) acetate (2.2 mg, 0.01 mmol) and tricyclohexylphosphine (5.6 mg, 0.02 mmol) was added and the
 10 reaction mixture was heated up to 100 °C for 16 hours. It was cooled down and partitioned between EtOAc and water. 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. MS (m/z) 509.8 $[M+H]^+$.

15 Synthesis of (S)-2-(2-(3,5-difluorophenyl)-1-(2-(5-hydroxy-1H-indol-3-yl)acetamido)ethyl)-3,4'-bipyridine-2'-carboxamide (**310C**):

Compound 310C was prepared according to the method presented for the synthesis of Example 20 294 substituting Compound 310B for Compound 377 to afford 4 mg of the title compound: MS (m/z) 528.2 $[M+H]^+$. 1H NMR (400 MHz, cd_3od) δ 8.51 (dd, $J = 14.7, 4.9$ Hz, 2H), 7.61 – 7.47 (m, 2H), 7.32 (dd, $J = 7.9, 4.8$ Hz, 2H), 7.08 (d, $J = 8.6$ Hz, 1H), 6.98 (s, 1H), 6.73 (d, $J = 2.0$ Hz, 1H), 6.62 – 6.47 (m, 2H), 6.13 (d, $J = 6.2$ Hz, 2H), 5.30 – 5.11 (m, 1H), 3.51 (s, 2H), 2.97 – 2.75 (m, 2H).

25 Example 311



30 Synthesis of ethyl 2-(7,7-difluoro-3-(trifluoromethyl)-4,5,6,7-tetrahydro-1H-indazol-1-yl)acetate (**311A**):

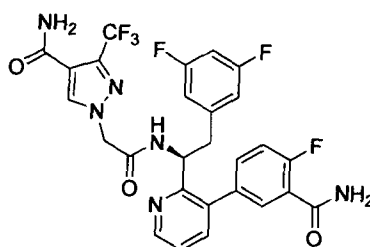
Compound 311A was prepared according to the method presented in the synthesis of Example 285E substituting Compound 272B for Compound 285C to afford the title compound. MS (m/z) 313.05 $[M+H]^+$.

5 Synthesis of (S)-5-(2-(1-(2-(7,7-difluoro-3-(trifluoromethyl)-4,5,6,7-tetrahydro-1H-indazol-1-yl)acetamido)-2-(3,5-difluorophenyl)ethyl)pyridin-3-yl)-2-fluorobenzamide (**311B**):

Compound 311B was prepared according to the method presented in the synthesis of Example 54 utilizing Compound 54B and ethyl ethyl 2-(7,7-difluoro-3-(trifluoromethyl)-4,5,6,7-tetrahydro-1H-indazol-1-yl)acetate to provide 43 mg of the title compound ; MS (m/z) 638.46

10 $[M+H]^+$. 1H NMR (400 MHz, cd_3od) δ 8.72 (dd, $J = 5.0, 1.6$ Hz, 1H), 7.71 (dd, $J = 7.8, 1.6$ Hz, 1H), 7.51 (dd, $J = 7.8, 5.0$ Hz, 1H), 7.44 – 7.27 (m, 2H), 7.22 (dd, $J = 10.7, 8.6$ Hz, 1H), 6.66 (tt, $J = 9.2, 2.3$ Hz, 1H), 6.31 (t, $J = 6.3$ Hz, 2H), 5.36 (t, $J = 7.6$ Hz, 1H), 5.15 – 4.97 (m, 2H), 3.05 (t, $J = 10.6$ Hz, 2H), 2.65 (s, 2H), 2.32 – 2.16 (m, 2H), 2.06 – 1.85 (m, 2H).

15 Example 312



312

Synthesis of (S)-1-(2-(1-(3-(3-carbamoyl-4-fluorophenyl)pyridin-2-yl)-2-(3,5-

20 difluorophenyl)ethylamino)-2-oxoethyl)-3-(trifluoromethyl)-1H-pyrazole-4-carboxamide (**312**):

To a solution of (S)-1-(2-(1-(3-(3-carbamoyl-4-fluorophenyl)pyridin-2-yl)-2-(3,5-

difluorophenyl)ethylamino)-2-oxoethyl)-3-(trifluoromethyl)-1H-pyrazole-4-carboxylic acid

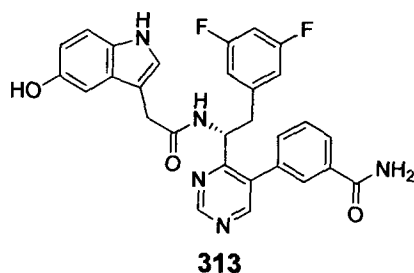
(**323**, 30 mg, 0.05 mmol) in 0.5 mL of DMF were added HOBt (10 mg, 0.075 mmol), 0.5 M

25 ammonia solution in 1,4-dioxane (0.5 mL, 0.25 mmol), N,N-diisopropylethylamine (26 μ L, 0.15

mmol), and HATU (29 mg, 0.075 mmol). After stirring for 2 hours at room temperature, It was partitioned between EtOAc and saturated $NaHCO_3$ aqueous solution. 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 10

mg of the title compound. MS (m/z) 591.34 $[M+H]^+$. 1H NMR (400 MHz, cd_3od) δ 8.70 – 8.56 (m, 1H), 8.09 (s, 1H), 7.47 (dd, $J = 7.8, 1.7$ Hz, 1H), 7.37 – 7.25 (m, 2H), 7.14 (m, 2H), 6.56 (t, $J = 9.3$ Hz, 1H), 6.22 (d, $J = 6.3$ Hz, 2H), 5.36 – 5.18 (m, 1H), 4.88 (s, 2H), 2.99 (m, 2H).

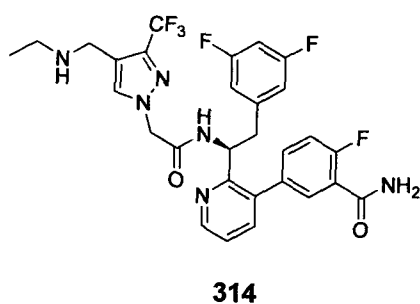
5 Example 313



Synthesis of (R)-3-(4-(2-(3,5-difluorophenyl)-1-(2-(5-hydroxy-1H-indol-3-yl)acetamido)ethyl)pyrimidin-5-yl)benzamide (**313**):

- 10 Compound 313 was prepared according to the method presented for the synthesis of Example 295B substituting Compound 279F and 3-carbamoylphenylboronic acid for Compound 295A and 3-sulfamoylphenylboronic acid to afford 19 mg of the title compound: MS (m/z) 528.4 $[M+H]^+$. 1H NMR (400 MHz, cd_3od) δ 9.13 (s, 1H), 8.54 (s, 1H), 7.94 (d, $J = 8.1$ Hz, 1H), 7.65 (s, 1H), 7.52 (t, $J = 7.6$ Hz, 1H), 7.37 (d, $J = 7.2$ Hz, 1H), 7.17 (d, $J = 8.8$ Hz, 1H), 7.06 (s, 1H),
 15 6.83 (s, 1H), 6.65 (t, $J = 10.3$ Hz, 2H), 6.27 (d, $J = 6.5$ Hz, 2H), 5.45 (t, $J = 7.4$ Hz, 1H), 3.71 – 3.50 (m, 2H), 2.97 (d, $J = 7.5$ Hz, 2H).

Example 314

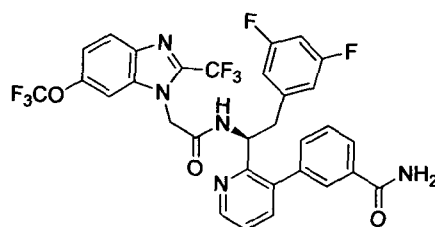


- 20 Synthesis of (S)-5-(2-(2-(3,5-difluorophenyl)-1-(2-(4-((ethylamino)methyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl)acetamido)ethyl)pyridin-3-yl)-2-fluorobenzamide (**314**):

Compound 314 was prepared according to the method presented for the synthesis of Example 333 substituting ethylamine hydrochloride for methylamine hydrochloride to afford 5 mg of the title compound: MS (m/z) 605.32 $[M+H]^+$. 1H NMR (400 MHz, cd_3od) δ 8.70 (dd, $J = 4.8, 1.6$

Hz, 1H), 7.94 (s, 1H), 7.57 (dd, $J = 7.8, 1.7$ Hz, 1H), 7.48 (d, $J = 5.0$ Hz, 1H), 7.39 (dd, $J = 7.8, 4.8$ Hz, 1H), 7.30 – 7.12 (m, 2H), 6.66 (dd, $J = 10.4, 8.1$ Hz, 1H), 6.33 (d, $J = 6.2$ Hz, 2H), 5.46 – 5.22 (m, 1H), 4.99 (s, 2H), 4.18 (s, 2H), 3.16 – 3.00 (m, 4H), 1.31 (t, $J = 7.3$ Hz, 3H).

5 Example 315

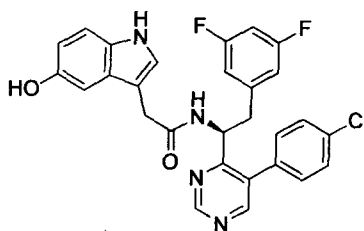


315

Synthesis of (S)-3-(2-(2-(3,5-difluorophenyl)-1-(2-(6-(trifluoromethoxy)-2-(trifluoromethyl)-1H-benzo[d]imidazol-1-yl)acetamido)ethyl)pyridin-3-yl)benzamide (**315**):

Compound **315** was prepared according to the method presented in the synthesis of Example 55F utilizing Compound **55D** and 2-(6-(trifluoromethoxy)-2-(trifluoromethyl)-1H-benzo[d]imidazol-1-yl)acetic acid to afford (S)-N-(1-(3-bromopyridin-2-yl)-2-(3,5-difluorophenyl)ethyl)-2-(6-(trifluoromethoxy)-2-(trifluoromethyl)-1H-benzo[d]imidazol-1-yl)acetamide and then Suzuki coupling with 3-carbamoylphenylboronic acid to provide 17 mg of the title compound. MS (m/z) 663.7 $[M+H]^+$. 1H NMR (400 MHz, cd_3od) δ 8.75 (d, $J = 4.9$ Hz, 1H), 7.86 (d, $J = 8.8$ Hz, 2H), 7.67 (d, $J = 7.8$ Hz, 1H), 7.55 (d, $J = 6.8$ Hz, 2H), 7.50 – 7.41 (m, 2H), 7.31 (dd, $J = 19.6, 8.3$ Hz, 2H), 6.67 (t, $J = 9.2$ Hz, 1H), 6.29 (d, $J = 6.3$ Hz, 2H), 5.44 (t, $J = 7.6$ Hz, 1H), 5.22 (s, 2H), 3.10 – 3.03 (m, 2H).

Example 316



316

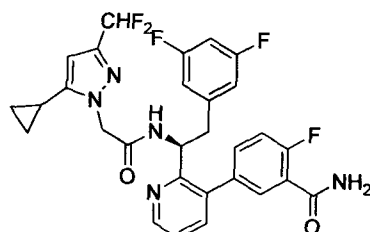
Synthesis of (S)-N-(1-(5-(4-chlorophenyl)pyrimidin-4-yl)-2-(3,5-difluorophenyl)ethyl)-2-(5-hydroxy-1H-indol-3-yl)acetamide (**316**):

Compound **316** was prepared according to the method presented for the synthesis of Example 279G substituting Compound **279D** and 2-(5-hydroxy-1H-indol-3-yl)acetic acid for Compound **279E** and 2-(5,6-dimethyl-1H-benzo[d]imidazol-1-yl)acetic acid to afford 12 mg of the title

compound: MS (m/z) 519.3 $[M+H]^+$. 1H NMR (400 MHz, cd_3od) δ 9.10 (s, 1H), 8.48 (s, 1H), 7.40 (d, $J = 8.2$ Hz, 2H), 7.15 (dd, $J = 17.5, 8.5$ Hz, 3H), 7.06 (s, 1H), 6.83 (s, 1H), 6.67 (d, $J = 9.2$ Hz, 2H), 6.30 (d, $J = 6.8$ Hz, 2H), 5.40 (t, $J = 7.6$ Hz, 1H), 3.68 – 3.51 (m, 2H), 2.96 (d, $J = 7.8$ Hz, 2H).

5

Example 317

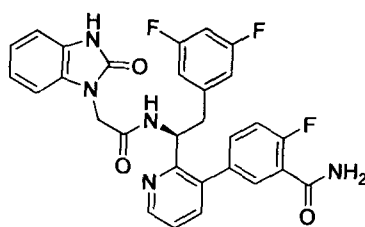


317

Synthesis of (S)-5-(2-(1-(2-(5-cyclopropyl-3-(difluoromethyl)-1H-pyrazol-1-yl)acetamido)-2-(3,5-difluorophenyl)ethyl)pyridin-3-yl)-2-fluorobenzamide (**317**):

Compound 317 was prepared according to the method presented in the synthesis of Example 56 utilizing Compound 56A and 5-cyclopropyl-3-(difluoromethyl)-1H-pyrazole to provide 36 mg of the title compound. MS (m/z) 570.34 $[M+H]^+$. 1H NMR (400 MHz, cd_3od) δ 8.70 (dd, $J = 4.9, 1.7$ Hz, 1H), 7.79 – 7.65 (m, 1H), 7.57 – 7.46 (m, 1H), 7.34 (s, 1H), 7.23 (dt, $J = 10.9, 4.3$ Hz, 1H), 6.73 – 6.42 (m, 2H), 6.32 (dd, $J = 18.4, 5.2$ Hz, 2H), 6.11 (s, 1H), 5.37 (dd, $J = 16.3, 8.8$ Hz, 1H), 4.95 (s, 2H), 3.10 – 2.93 (m, 2H), 1.71 – 1.57 (m, 1H), 0.97 – 0.80 (m, 2H), 0.72 – 0.55 (m, 2H).

Example 318



318

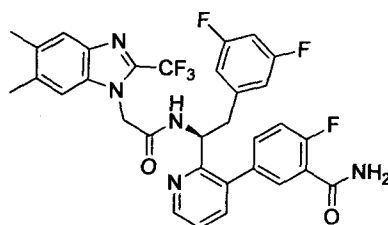
Synthesis of (S)-5-(2-(2-(3,5-difluorophenyl)-1-(2-(2-oxo-2,3-dihydro-1H-benzo[d]imidazol-1-yl)acetamido)ethyl)pyridin-3-yl)-2-fluorobenzamide (**318**):

Compound 318 was prepared according to the method presented for the synthesis of Example 332 substituting 1H-benzo[d]imidazol-2(3H)-one for 2-chloropyridin-4-ol to afford 10 mg of the

title compound: MS (*m/z*) 546.37 [*M*+*H*]⁺. ¹H NMR (400 MHz, *cd*₃od) δ 8.63 (dd, *J* = 5.0, 1.6 Hz, 1H), 7.63 (dd, *J* = 7.8, 1.6 Hz, 1H), 7.46 – 7.20 (m, 3H), 7.13 (dd, *J* = 10.7, 8.5 Hz, 1H), 7.02 – 6.87 (m, 3H), 6.77 (d, *J* = 7.0 Hz, 1H), 6.64 – 6.52 (m, 1H), 6.26 (d, *J* = 6.1 Hz, 2H), 5.31 (t, *J* = 7.6 Hz, 1H), 4.76 (s, 12H), 3.12 – 2.83 (m, 2H).

5

Example 319



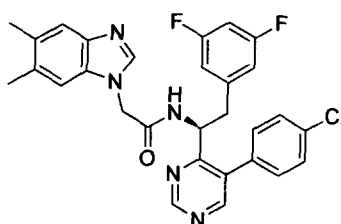
319

Synthesis of (S)-5-(2-(2-(3,5-difluorophenyl)-1-(2-(5,6-dimethyl-2-(trifluoromethyl)-1H-benzo[d]imidazol-1-yl)acetamido)ethyl)pyridin-3-yl)-2-fluorobenzamide (**319**):

Compound 319 was prepared according to the method presented in the synthesis of Example 54 utilizing Compound 54B and 2-(5,6-dimethyl-2-(trifluoromethyl)-1H-benzo[d]imidazol-1-yl)acetic acid to provide 11 mg of the title compound. MS (*m/z*) 625.5 [*M*+*H*]⁺. ¹H NMR (400 MHz, *cd*₃od) δ 8.73 (d, *J* = 4.7 Hz, 1H), 7.57 (d, *J* = 7.8 Hz, 1H), 7.52 (s, 1H), 7.40 (dd, *J* = 7.7, 4.9 Hz, 2H), 7.30 (s, 1H), 7.23 (s, 1H), 7.21 – 7.11 (m, 1H), 6.68 (t, *J* = 9.3 Hz, 1H), 6.35 (d, *J* = 6.4 Hz, 2H), 5.35 (t, *J* = 7.5 Hz, 1H), 5.19 – 5.00 (m, 2H), 3.15 – 2.98 (m, 2H), 2.38 (s, 6H).

15

Example 320



320

Synthesis of (S)-N-(1-(5-(4-chlorophenyl)pyrimidin-4-yl)-2-(3,5-difluorophenyl)ethyl)-2-(5,6-dimethyl-1H-benzo[d]imidazol-1-yl)acetamide (**320**):

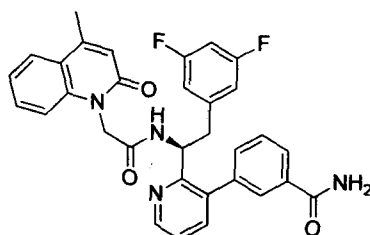
Compound 320 was prepared according to the method presented for the synthesis of Example 316 substituting 2-(5,6-dimethyl-1H-benzo[d]imidazol-1-yl)acetic acid for 2-(5-hydroxy-1H-

25

indol-3-yl)acetic acid to afford 11 mg of the title compound: MS (m/z) 531.9 $[M+H]^+$. 1H NMR (400 MHz, cd_3od) δ 9.23 (d, $J = 13.3$ Hz, 2H), 8.54 (s, 1H), 7.59 (s, 1H), 7.46 – 7.36 (m, 3H), 7.18 (d, $J = 8.0$ Hz, 2H), 6.74 (t, $J = 9.1$ Hz, 1H), 6.38 (d, $J = 6.8$ Hz, 2H), 5.45 (d, $J = 7.2$ Hz, 1H), 5.25 (s, 2H), 3.08 (m, 2H), 2.45 (s, 6H).

5

Example 321

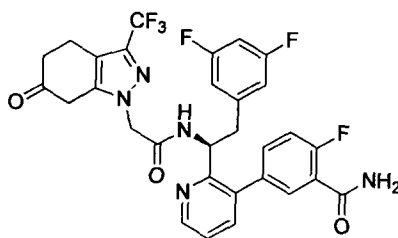


321

Synthesis of (S)-3-(2-(2-(3,5-difluorophenyl)-1-(2-(4-methyl-2-oxoquinolin-1(2H)-yl)acetamido)ethyl)pyridin-3-yl)benzamide (**321**):

- 10 Compound 321 was prepared according to the method presented in the synthesis of Example 55 utilizing Compound 55D and 2-(4-methyl-2-oxoquinolin-1(2H)-yl)acetic acid to afford (S)-N-(1-(3-bromopyridin-2-yl)-2-(3,5-difluorophenyl)ethyl)-2-(4-methyl-2-oxoquinolin-1(2H)-yl)acetamide, and then Suzuki coupling with 3-carbamoylphenylboronic acid to provide 18 mg
- 15 of the title compound. MS (m/z) 553.0 $[M+H]^+$. 1H NMR (400 MHz, cd_3od) δ 8.83 – 8.68 (m, 1H), 7.87 (dd, $J = 12.7, 7.9$ Hz, 2H), 7.80 – 7.69 (m, 1H), 7.62 (s, 1H), 7.59 – 7.41 (m, 3H), 7.38 – 7.15 (m, 3H), 6.67 (t, $J = 9.3$ Hz, 1H), 6.60 (s, 1H), 6.30 (d, $J = 6.2$ Hz, 2H), 5.48 (t, $J = 7.6$ Hz, 1H), 5.21 – 5.02 (m, 2H), 3.12 – 2.97 (m, 2H), 2.51 (s, 3H).

Example 322



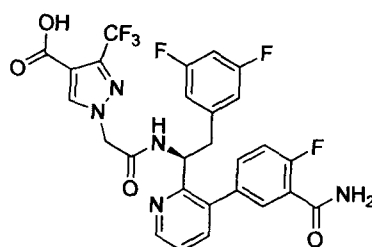
322

20 Synthesis of (S)-5-(2-(2-(3,5-difluorophenyl)-1-(2-(6-oxo-3-(trifluoromethyl)-4,5,6,7-tetrahydro-1H-indazol-1-yl)acetamido)ethyl)pyridin-3-yl)-2-fluorobenzamide (**322**):

Compound 322 was prepared according to the method presented for the synthesis of Example 60H substituting 3-ethoxycyclohex-2-enone for bicyclo[3.1.0]hexan-3-one to afford 8 mg of the

title compound: MS (m/z) 616.02 [M+H]⁺. ¹H NMR (400 MHz, cdcl₃) δ 9.99 (d, *J* = 7.2 Hz, 1H), 8.81 (d, *J* = 5.6 Hz, 1H), 8.13 – 8.01 (m, 1H), 7.83 (dd, *J* = 7.9, 5.6 Hz, 2H), 7.60 (m, 1H), 7.30 (dd, *J* = 11.2, 8.6 Hz, 1H), 6.98 (s, 2H), 6.62 (t, *J* = 8.9 Hz, 1H), 6.20 (d, *J* = 5.6 Hz, 2H), 5.48 (dd, *J* = 16.4, 7.2 Hz, 1H), 4.80 (q, *J* = 16.7 Hz, 2H), 3.37 (q, *J* = 20.3 Hz, 2H), 3.22 (dd, *J* = 13.6, 6.8 Hz, 1H), 3.07 – 2.86 (m, 3H), 2.66 (t, *J* = 6.8 Hz, 2H).

Example 323

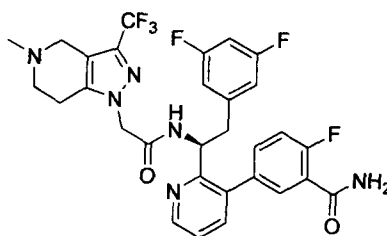


323

Synthesis of (S)-1-(2-(1-(3-(3-carbamoyl-4-fluorophenyl)pyridin-2-yl)-2-(3,5-difluorophenyl)ethylamino)-2-oxoethyl)-3-(trifluoromethyl)-1H-pyrazole-4-carboxylic acid (**323**):

Compound 289 (352 mg, 0.57 mmol) was dissolved in 10 mL of THF/MeOH/H₂O (3/2/1) and to it was added LiOH·H₂O (119 mg, 2.8 mmol). The mixture was stirred at ambient temperature for 16 hours. It was acidified at 0 °C with 1N HCl and extracted with EtOAc. The organic layer was separated, dried over MgSO₄, filtered and concentrated. The residue was purified by reverse phase HPLC eluting with acetonitrile/water (with 0.1% TFA) to afford 256 mg of the title compound. MS (m/z) 592.25 [M+H]⁺. ¹H NMR (400 MHz, cd₃od) δ 8.71 (dd, *J* = 4.9, 1.6 Hz, 1H), 8.26 (s, 1H), 7.66 (dd, *J* = 7.8, 1.6 Hz, 1H), 7.51 – 7.40 (m, 2H), 7.34 (s, 1H), 7.22 (dd, *J* = 10.7, 8.6 Hz, 1H), 6.65 (dd, *J* = 10.3, 8.1 Hz, 1H), 6.31 (d, *J* = 6.2 Hz, 2H), 5.35 (t, *J* = 7.6 Hz, 1H), 4.99 (s, 2H), 3.08 (d, *J* = 7.6 Hz, 2H).

Example 324

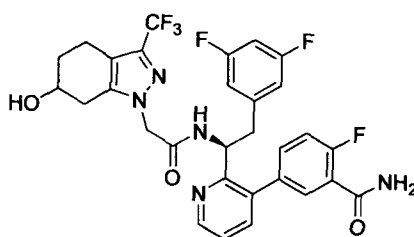


324

Synthesis of (S)-5-(2-(2-(3,5-difluorophenyl)-1-(2-(5-methyl-3-(trifluoromethyl)-4,5,6,7-tetrahydro-1H-pyrazolo[4,3-c]pyridin-1-yl)acetamido)ethyl)pyridin-3-yl)-2-fluorobenzamide (324):

Compound 303 (30 mg, 0.05 mmol) was dissolved in 1 mL of 1,2-dichloroethane. To it was added formic acid solution (40 % in water, 15 mg, 0.5 mmol) and acetic acid (29 μ L, 0.5 mmol). After stirring at ambient temperature for 20 min, NaBH(OAc)₃ (16 mg, 0.15 mmol) was added, and the reaction mixture was stirred for 10 min. The reaction was quenched by adding NaHCO₃ (saturated aqueous solution), and extracted by EtOAc. The organic layer was separated, washed with half brine, dried over MgSO₄ and filtered. The filtrate was concentrated and purified by reverse phase HPLC eluting with acetonitrile/water (with 0.1% TFA) to afford 19.1 mg of the title compound. MS (m/z) 617.39 [M+H]⁺. ¹H NMR (400 MHz, cd₃od) δ 8.71 (dd, *J* = 4.8, 1.6 Hz, 1H), 7.64 – 7.58 (m, 1H), 7.53 (d, *J* = 6.4 Hz, 1H), 7.41 (dd, *J* = 7.8, 4.8 Hz, 1H), 7.27 – 7.12 (m, 2H), 6.67 (t, *J* = 9.2 Hz, 1H), 6.34 (d, *J* = 6.2 Hz, 2H), 5.42 – 5.25 (m, 1H), 4.94 (s, 2H), 4.29 (bs, 2H), 3.52 (bs, 2H), 3.20 – 2.93 (m, 7H).

Example 325

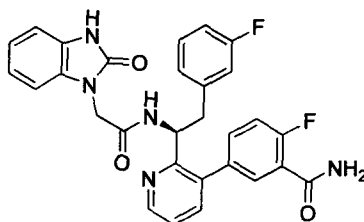


325

Synthesis of 5-(2-((1S)-2-(3,5-difluorophenyl)-1-(2-(6-hydroxy-3-(trifluoromethyl)-4,5,6,7-tetrahydro-1H-indazol-1-yl)acetamido)ethyl)pyridin-3-yl)-2-fluorobenzamide (325):

Compound 322 (30 mg, 0.049 mmol) was dissolved in 2 mL of CH₂Cl₂ and 1 mL of isopropanol. To it was added NaBH₄ (36 mg, 0.98 mmol) and the resulting mixture was stirred at ambient temperature for 4 hours. The reaction was quenched by adding NaHCO₃ (saturated aqueous solution), and extracted by EtOAc. The organic layer was separated, washed with half brine, dried over MgSO₄ and filtered. The filtrate was concentrated and purified by reverse phase HPLC eluting with acetonitrile/water (with 0.1% TFA) to afford 19.1 mg of the title compound. MS (m/z) 618.51 [M+H]⁺. ¹H NMR (400 MHz, cd₃od) δ 8.71 (dd, *J* = 4.9, 1.6 Hz, 1H), 7.68 (m, 1H), 7.47 (m, 2H), 7.32 (s, 1H), 7.26 – 7.07 (m, 1H), 6.79 – 6.58 (m, 1H), 6.32 (t, *J* = 7.1 Hz, 2H), 5.36 (q, *J* = 7.4 Hz, 1H), 4.81 (s, 2H), 4.13 (d, *J* = 5.7 Hz, 1H), 3.06 (d, *J* = 7.7 Hz, 2H), 2.87 – 2.64 (m, 2H), 2.65 – 2.37 (m, 2H), 1.82 (m, 2H).

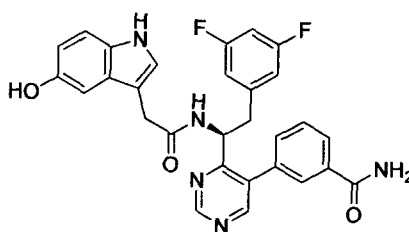
Example 326

**326**

Synthesis of (S)-2-fluoro-5-(2-(2-(3-fluorophenyl)-1-(2-(2-oxo-2,3-dihydro-1H-benzo[d]imidazol-1-yl)acetamido)ethyl)pyridin-3-yl)benzamide (**326**):

Compound **326** was prepared according to the method presented in the synthesis of Example 59 utilizing Compound 59D and 2-(2-oxo-2,3-dihydro-1H-benzo[d]imidazol-1-yl)acetic acid to provide 21 mg of the title compound. MS (m/z) 528.35 $[M+H]^+$. 1H NMR (400 MHz, cd_3od) δ 8.72 (dd, $J = 5.0, 1.5$ Hz, 1H), 7.71 (dd, $J = 7.8, 1.6$ Hz, 1H), 7.52 (dd, $J = 7.8, 5.0$ Hz, 1H), 7.32 (d, $J = 6.3$ Hz, 2H), 7.17 (dd, $J = 10.6, 8.7$ Hz, 1H), 7.11 – 6.94 (m, 4H), 6.91 – 6.79 (m, 2H), 6.48 (dd, $J = 22.6, 8.5$ Hz, 2H), 5.40 – 5.31 (m, 1H), 4.56 (s, 2H), 3.17 – 2.95 (m, 2H).

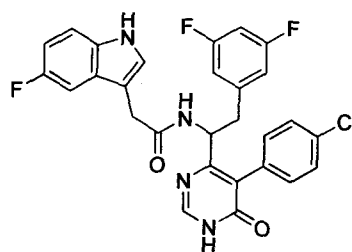
15 Example 327

**327**

Synthesis of (S)-3-(4-(2-(3,5-difluorophenyl)-1-(2-(5-hydroxy-1H-indol-3-yl)acetamido)ethyl)pyrimidin-5-yl)benzamide (**327**):

Compound **327** was prepared according to the method presented for the synthesis of Example 295B substituting 3-carbamoylphenylboronic acid for 3-sulfamoylphenylboronic acid to afford 20 mg of the title compound: MS (m/z) 528.1 $[M+H]^+$. 1H NMR (400 MHz, cd_3od) δ 9.13 (s, 1H), 8.54 (s, 1H), 7.94 (d, $J = 7.5$ Hz, 1H), 7.65 (s, 1H), 7.52 (t, $J = 7.9$ Hz, 1H), 7.37 (d, $J = 7.7$ Hz, 1H), 7.17 (d, $J = 8.6$ Hz, 1H), 7.06 (s, 1H), 6.83 (s, 1H), 6.65 (t, $J = 10.4$ Hz, 2H), 6.27 (d, $J = 6.8$ Hz, 2H), 5.45 (t, $J = 7.7$ Hz, 1H), 3.71 – 3.51 (m, 2H), 2.97 (d, $J = 7.5$ Hz, 2H).

Example 328

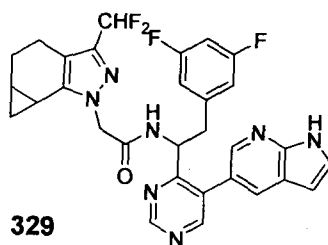
**328**

- 5 Synthesis of N-(1-(5-(4-chlorophenyl)-6-oxo-1,6-dihydropyrimidin-4-yl)-2-(3,5-difluorophenyl)ethyl)-2-(5-fluoro-1H-indol-3-yl)acetamide (**328**):

Compound **328** was prepared according to the method presented for the synthesis of Example 301B substituting 2-(5-fluoro-1H-indol-3-yl)acetic acid for 2-(3-(trifluoromethyl)-4,5,6,7-tetrahydro-1H-indazol-1-yl)acetic acid to afford 4 mg of the title compound: MS (m/z) 537.1

- 10 $[M+H]^+$. 1H NMR (400 MHz, $cdCl_3$) δ 9.77 (s, 1H), 8.33 (s, 2H), 7.30 (dt, $J = 9.8, 5.0$ Hz, 1H), 7.24 – 7.11 (m, 2H), 7.07 – 6.89 (m, 3H), 6.84 (dd, $J = 14.5, 8.3$ Hz, 2H), 6.58 (d, $J = 8.8$ Hz, 1H), 6.82 (d, $J = 8.2$ Hz, 2H), 5.83 (d, $J = 6.9$ Hz, 1H), 4.93 – 4.76 (m, 1H), 3.72 – 3.46 (m, 2H), 2.58 (dd, $J = 14.4, 4.7$ Hz, 1H), 1.97 (dd, $J = 14.4, 10.9$ Hz, 1H).

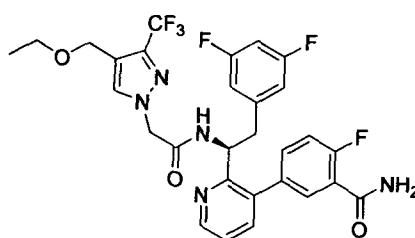
15 Example 329

**329**

Compound 299D was purified by chiral column chromatography using aCHIRALPAK IC column eluting with heptane:ethanol (80:20). The slowest eluent (3rd peak) was collected, concentrated and high vacuum dried to provide 10 mg of the title compound as a single

- 20 diastereomer. MS (m/z) 576.07 $[M+H]^+$. 1H NMR (400 MHz, cd_3od) δ 9.20 (s, 1H), 8.60 (s, 1H), 7.95 (d, $J = 2.0$ Hz, 1H), 7.81 (d, $J = 1.9$ Hz, 1H), 7.46 (d, $J = 3.5$ Hz, 1H), 6.69 (m, 1H), 6.51 (dd, $J = 29.0, 25.6$ Hz, 2H), 6.32 (d, $J = 6.2$ Hz, 2H), 5.48 (t, $J = 7.4$ Hz, 1H), 4.87 (s, 2H), 3.14 – 2.93 (m, 2H), 2.70 (dd, $J = 15.5, 5.5$ Hz, 1H), 2.23 – 1.96 (m, 2H), 1.81 – 1.67 (m, 2H), 1.60 (m, 1H), 0.90 (m, 1H), 0.65 (dd, $J = 10.4, 4.9$ Hz, 1H).

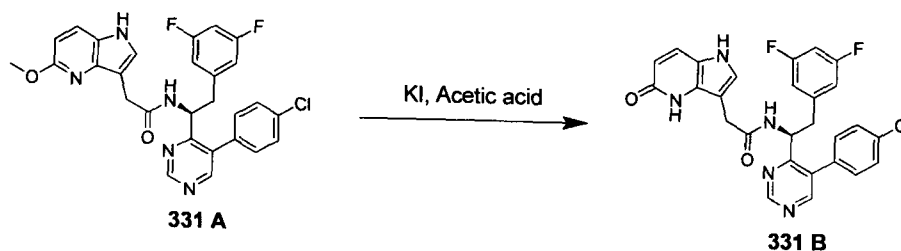
Example 330

**330**

- 5 Synthesis of (S)-5-(2-(2-(3,5-difluorophenyl)-1-(2-(4-(ethoxymethyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl)acetamido)ethyl)pyridin-3-yl)-2-fluorobenzamide (**330**):

Compound 330 was prepared according to the method presented for the synthesis of Example 361 substituting ethanol for methanol to afford 14 mg of the title compound: MS (m/z) 606.31 [M+H]⁺. ¹H NMR (400 MHz, cd₃od) δ 8.70 (dd, J = 4.9, 1.6 Hz, 1H), 7.74 (s, 1H), 7.66 (dd, J = 7.8, 1.6 Hz, 1H), 7.51 – 7.38 (m, 2H), 7.37 – 7.10 (m, 2H), 6.66 (dd, J = 10.3, 8.1 Hz, 1H), 6.31 (d, J = 6.2 Hz, 2H), 5.35 (t, J = 7.6 Hz, 1H), 4.92 (s, 2H), 4.44 (s, 2H), 3.58 – 3.42 (m, 2H), 3.16 – 3.02 (m, 2H), 1.17 (t, J = 7.0 Hz, 3H).

Example 331



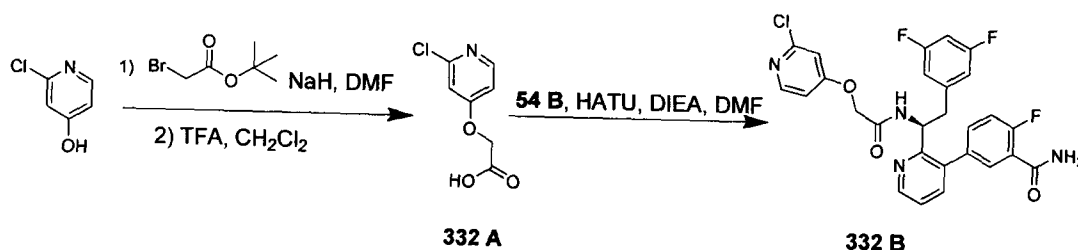
Synthesis of (S)-N-(1-(5-(4-chlorophenyl)pyrimidin-4-yl)-2-(3,5-difluorophenyl)ethyl)-2-(5-methoxy-1H-pyrrolo[3,2-b]pyridin-3-yl)acetamide (**331A**):

- 20 Compound 331A was prepared according to the method presented for the synthesis of Example 316 substituting 2-(5-methoxy-1H-pyrrolo[3,2-b]pyridin-3-yl)acetic acid for 2-(5-hydroxy-1H-indol-3-yl)acetic acid to afford the title compound. MS (m/z) 534.1 [M+H]⁺.

- 25 Synthesis of (S)-N-(1-(5-(4-chlorophenyl)pyrimidin-4-yl)-2-(3,5-difluorophenyl)ethyl)-2-(5-oxo-4,5-dihydro-1H-pyrrolo[3,2-b]pyridin-3-yl)acetamide (**331B**):

Compound 331A (18 mg, 0.034 mmol) was dissolved in 1 mL of acetic acid and to it was added KI (22 mg, 0.14 mmol). The reaction mixture was heated up to 160 °C in a Biotage® Initiator Microwave Synthesizer for 10min. It was cooled down and the solvent was removed. The residue was purified by reverse phase HPLC eluting with acetonitrile/water (with 0.1% TFA) to afford 4.1 mg of the title compound. MS (m/z) 520.1 $[M+H]^+$. 1H NMR (300 MHz, cd_3od) δ 9.09 (s, 1H), 8.44 (s, 1H), 8.01 (d, J = 9.0 Hz, 1H), 7.34 (d, J = 8.7 Hz, 3H), 7.13 (d, J = 8.5 Hz, 2H), 6.64 – 6.47 (m, 2H), 6.32 – 6.15 (m, 2H), 5.36 (t, J = 7.5 Hz, 1H), 3.65 – 3.51 (m, 2H), 2.91 (d, J = 7.6 Hz, 2H).

Example 332



Synthesis of 2-(2-chloropyridin-4-yloxy)acetic acid (**332A**):

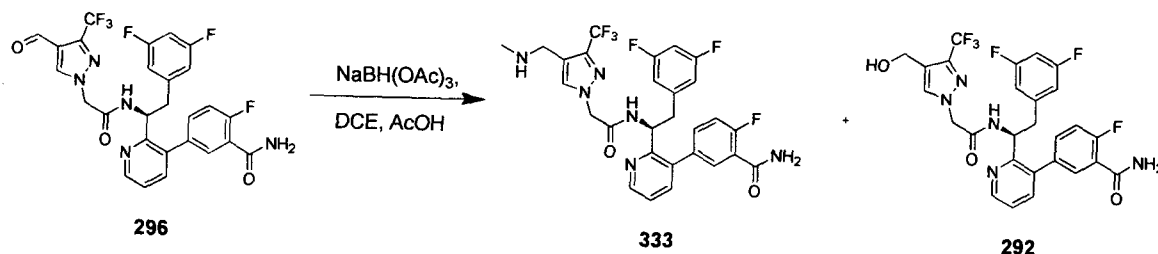
2-chloropyridin-4-ol (500 mg, 3.9 mmol) was dissolved in 10 mL of DMF and cooled down to 0 °C. To it was added NaH (60% in oil dispersion, 187 mg, 4.68 mmol) portionwise. The mixture was stirred at ambient temperature for 20 min, a solution of tert-butyl 2-bromoacetate (683 μ L, 4.68 mmol) was added dropwise. It was stirred for 20 min and quenched with saturated aqueous NH_4Cl solution. The mixture was partitioned between EtOAc and water. The organic layer was separated, dried over $MgSO_4$, filtered and concentrated. The residue was purified by silica gel chromatography eluting with EtOAc/Hexanes to afford 742 mg of tert-butyl 2-(2-chloropyridin-4-yloxy)acetate which was dissolved in 4 mL of 40 % of TFA/ CH_2Cl_2 and a drop of water. The reaction mixture was stirred at ambient temperature for 16 hours. The solvent was removed to provide the title compound. MS (m/z) 188.15 $[M+H]^+$.

Synthesis of (S)-5-(2-(1-(2-(2-chloropyridin-4-yloxy)acetamido)-2-(3,5-difluorophenyl)ethyl)pyridin-3-yl)-2-fluorobenzamide (**332B**):

Compound 332B was prepared according to the method presented in the synthesis of Example 54 utilizing Compound 54B and 2-(2-chloropyridin-4-yloxy)acetic acid to provide 7 mg of the

title compound. MS (m/z) 541.75 $[M+H]^+$. 1H NMR (400 MHz, cd_3od) δ 8.70 (dd, $J = 4.9, 1.6$ Hz, 1H), 8.16 (d, $J = 5.9$ Hz, 1H), 7.69 (dd, $J = 7.8, 1.6$ Hz, 1H), 7.55 – 7.44 (m, 2H), 7.36 (s, 1H), 7.25 (dd, $J = 10.7, 8.5$ Hz, 1H), 7.04 (d, $J = 2.3$ Hz, 1H), 6.95 (dd, $J = 5.9, 2.3$ Hz, 1H), 6.74 – 6.60 (m, 1H), 6.34 (d, $J = 6.2$ Hz, 2H), 5.43 (t, $J = 7.6$ Hz, 1H), 4.67 (s, 2H), 3.13 – 2.97 (m, 2H).

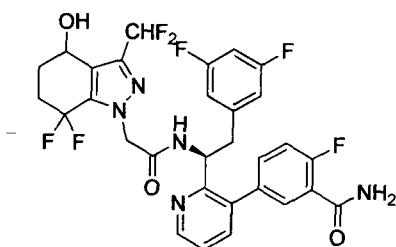
Example 333



Synthesis of (S)-5-(2-(2-(3,5-difluorophenyl)-1-(2-(4-((methylamino)methyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl)acetamido)ethyl)pyridin-3-yl)-2-fluorobenzamide (333):

To a mixture of (S)-5-(2-(2-(3,5-difluorophenyl)-1-(2-(4-formyl-3-(trifluoromethyl)-1H-pyrazol-1-yl)acetamido)ethyl)pyridin-3-yl)-2-fluorobenzamide (296, 20 mg, 0.035 mmol) and methylamine hydrochloride (5 mg, 0.07 mmol) was added 1 mL of 1,2-dichloroethane followed by 10 μ L of acetic acid. After the reaction mixture was stirred at ambient temperature for 10 min, $NaBH(OAc)_3$ (9 mg, 0.042 mmol) was added, and the reaction mixture was stirred for 16 hours. The reaction was quenched by adding $NaHCO_3$ (saturated aqueous solution), and extracted by EtOAc. The organic layer was separated, washed with half brine, dried over $MgSO_4$ and filtered. The filtrate was concentrated and purified by reverse phase HPLC eluting with acetonitrile/water (with 0.1% TFA) to afford 9 mg of (S)-5-(2-(2-(3,5-difluorophenyl)-1-(2-(4-(hydroxymethyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl)acetamido)ethyl)pyridin-3-yl)-2-fluorobenzamide as a side product and 6 mg of the title compound. MS (m/z) 591.32 $[M+H]^+$. 1H NMR (400 MHz, cd_3od) δ 8.70 (dd, $J = 4.7, 1.6$ Hz, 1H), 7.94 (s, 1H), 7.57 (dd, $J = 7.8, 1.7$ Hz, 1H), 7.48 (d, $J = 7.0$ Hz, 1H), 7.39 (dd, $J = 7.8, 4.8$ Hz, 1H), 7.26 (s, 1H), 7.24 – 7.14 (m, 1H), 6.66 (t, $J = 9.2$ Hz, 1H), 6.32 (d, $J = 6.1$ Hz, 2H), 5.40 – 5.21 (m, 1H), 4.99 (s, 2H), 4.19 (s, 2H), 3.08 (qd, $J = 13.2, 7.7$ Hz, 2H), 2.70 (s, 3H).

Example 334

**334**

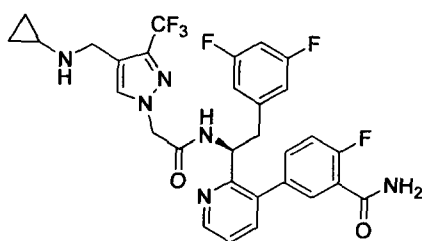
Synthesis of 5-(2-((1S)-1-(2-(3-(difluoromethyl)-7,7-difluoro-4-hydroxy-4,5,6,7-tetrahydro-1H-indazol-1-yl)acetamido)-2-(3,5-difluorophenyl)ethyl)pyridin-3-yl)-2-fluorobenzamide (**334**):

Compound 334 was prepared according to the method presented for the synthesis of Example

- 5 325 substituting Compound 285G for Compound 322 to afford 12 mg of the title compound: MS (m/z) 636.41 [M+H]⁺. ¹H NMR (400 MHz, cd₃od) δ 8.71 (d, *J* = 4.8 Hz, 1H), 7.74 – 7.59 (m, 1H), 7.52 – 7.43 (m, 1H), 7.40 – 7.14 (m, 3H), 7.04 – 6.60 (m, 2H), 6.30 (d, *J* = 7.7 Hz, 2H), 5.35 (t, *J* = 7.5 Hz, 1H), 5.01 (s, 2H), 4.90 (s, 1H), 3.07 (m, 2H), 2.52 (m, 1H), 2.18 (m, 2H), 1.95 (m, 1H).

10

Example 335

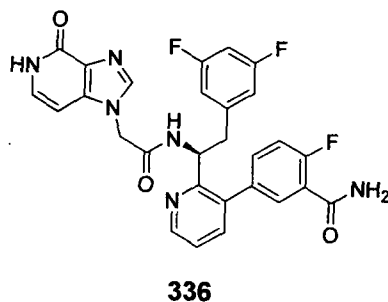
**335**

- 15 Synthesis of (S)-5-(2-(1-(2-(4-((cyclopropylamino)methyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl)acetamido)-2-(3,5-difluorophenyl)ethyl)pyridin-3-yl)-2-fluorobenzamide (**335**):

Compound 335 was prepared according to the method presented for the synthesis of Example 333 substituting cyclopropanamine for methylamine hydrochloride to afford 10 mg of the title

- 20 compound: MS (m/z) 617.30 [M+H]⁺. ¹H NMR (400 MHz, cd₃od) δ 8.70 (dd, *J* = 4.8, 1.6 Hz, 1H), 7.94 (s, 1H), 7.58 (dd, *J* = 7.8, 1.7 Hz, 1H), 7.48 (d, *J* = 4.9 Hz, 1H), 7.40 (dd, *J* = 7.8, 4.8 Hz, 1H), 7.33 – 7.10 (m, 2H), 6.72 – 6.55 (m, 1H), 6.33 (d, *J* = 6.1 Hz, 2H), 5.32 (dd, *J* = 8.4, 6.6 Hz, 1H), 4.99 (s, 2H), 4.30 (s, 2H), 3.08 (qd, *J* = 13.0, 7.6 Hz, 2H), 2.85 – 2.68 (m, 1H), 0.99 – 0.73 (m, 4H).

Example 336

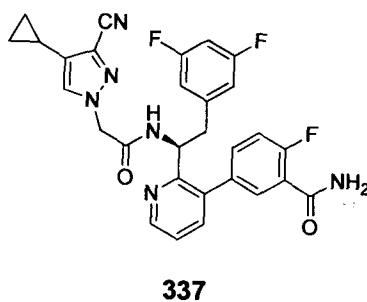


- 5 Synthesis of (S)-5-(2-(2-(3,5-difluorophenyl)-1-(2-(4-oxo-4,5-dihydro-1H-imidazo[4,5-c]pyridin-1-yl)acetamido)ethyl)pyridin-3-yl)-2-fluorobenzamide (**336**):

Compound 336 was prepared according to the method presented for the synthesis of Example 282 substituting Compound 368 for Compound 332 to afford 6 mg of the title compound: MS (m/z) 547.26 [M+H]⁺. ¹H NMR (400 MHz, cd₃od) δ 8.71 (dd, J = 4.8, 1.6 Hz, 1H), 8.56 (s, 1H), 7.64 – 7.56 (m, 1H), 7.50 (d, J = 5.2 Hz, 1H), 7.45 – 7.38 (m, 1H), 7.36 – 7.12 (m, 3H), 6.80 – 6.54 (m, 2H), 6.32 (dd, J = 18.2, 6.3 Hz, 2H), 5.38 – 5.30 (m, 1H), 5.07 (s, 2H), 3.17 – 2.99 (m, 2H).

Example 337

15



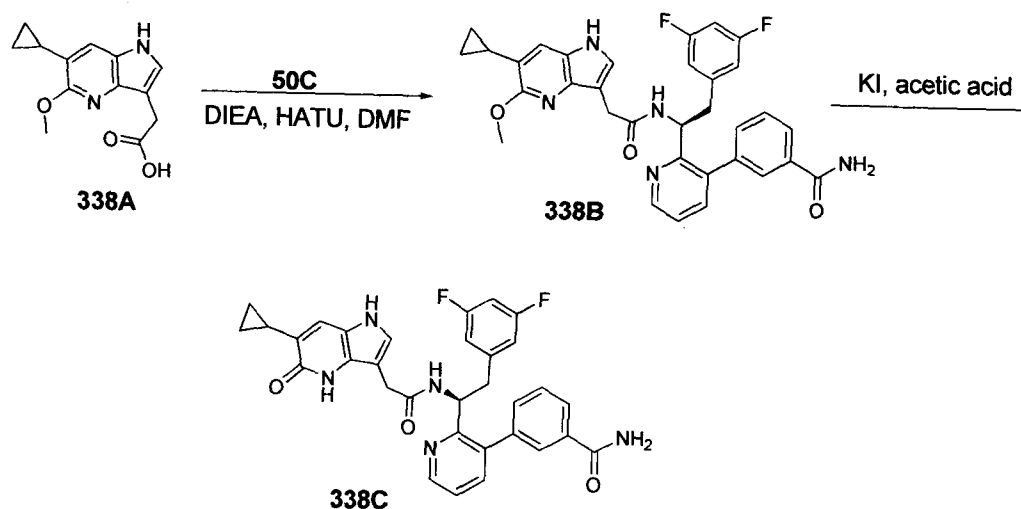
Synthesis of (S)-5-(2-(1-(2-(3-cyano-4-cyclopropyl-1H-pyrazol-1-yl)acetamido)-2-(3,5-difluorophenyl)ethyl)pyridin-3-yl)-2-fluorobenzamide (**337**):

- 20 Compound 337 was prepared according to the method presented for the synthesis of Example 276 substituting Compound 359 for Compound 463 to afford 5 mg of the title compound: MS (m/z) 545.29 [M+H]⁺. ¹H NMR (400 MHz, cd₃od) δ 8.69 (dd, J = 4.8, 1.6 Hz, 1H), 7.59 (dd, J = 7.8, 1.7 Hz, 1H), 7.47 – 7.37 (m, 3H), 7.35 – 7.10 (m, 2H), 6.65 (t, J = 9.2 Hz, 1H), 6.30 (d, J =

6.1 Hz, 2H), 5.36 – 5.21 (m, 1H), 4.88 – 4.84 (m, 2H), 3.13 – 2.85 (m, 2H), 1.88 – 1.49 (m, 1H), 1.00 – 0.88 (m, 2H), 0.72 – 0.61 (m, 2H).

Example 338

5



Synthesis of 2-(6-cyclopropyl-5-methoxy-1H-pyrrolo[3,2-b]pyridin-3-yl)acetic acid (**338A**):

Compound 338A was prepared according to the method presented for the synthesis of Example

10 360D substituting cyclopropylboronic acid for methyl boronic acid to afford the title compound: MS (*m/z*) 245.0 [*M*-H]⁻.

Synthesis of (S)-3-(2-(1-(2-(6-cyclopropyl-5-methoxy-1H-pyrrolo[3,2-b]pyridin-3-yl)acetamido)-2-(3,5-difluorophenyl)ethyl)pyridin-3-yl)benzamide (**338B**):

15 Compound 338B was prepared according to the method presented in the synthesis of Example 50 utilizing Compound 50C and Compound 338A to provide the title compound. MS (*m/z*) 582.1 [*M*+H]⁺.

Synthesis of (S)-3-(2-(1-(2-(6-cyclopropyl-5-oxo-4,5-dihydro-1H-pyrrolo[3,2-b]pyridin-3-yl)acetamido)-2-(3,5-difluorophenyl)ethyl)pyridin-3-yl)benzamide (**338C**):

Compound 338C was prepared according to the method presented for the synthesis of Example 331 substituting Compound 338B for Compound 331A to afford 4 mg of the title compound:

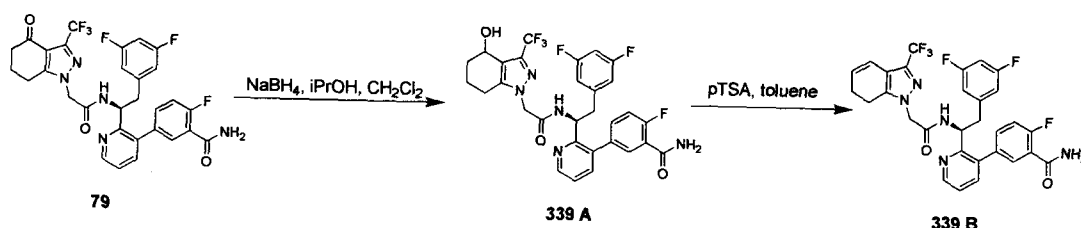
MS (*m/z*) 568.1 [*M*+H]⁺. ¹H NMR (400 MHz, cd₃od) δ 8.64 (d, *J* = 3.7 Hz, 1H), 7.89 (d, *J* = 7.8 Hz, 1H), 7.70 (s, 1H), 7.58 (d, *J* = 6.7 Hz, 1H), 7.47 (t, *J* = 7.7 Hz, 1H), 7.42 – 7.17 (m, 3H), 7.00 (s, 1H), 6.55 (t, *J* = 9.1 Hz, 1H), 6.21 (d, *J* = 6.5 Hz, 2H), 5.46 (dd, *J* = 13.6, 6.2 Hz, 1H),

25 7.00 (s, 1H), 6.55 (t, *J* = 9.1 Hz, 1H), 6.21 (d, *J* = 6.5 Hz, 2H), 5.46 (dd, *J* = 13.6, 6.2 Hz, 1H),

3.57 (s, 2H), 2.97 (ddd, $J = 19.9, 13.0, 7.5$ Hz, 2H), 2.20 – 1.96 (m, 1H), 1.05 – 0.81 (m, 2H), 0.59 (q, $J = 5.5$ Hz, 2H).

Example 339

5



Synthesis of 5-(2-((1S)-2-(3,5-difluorophenyl)-1-(2-(4-hydroxy-3-(trifluoromethyl)-4,5,6,7-tetrahydro-1H-indazol-1-yl)acetamido)ethyl)pyridin-3-yl)-2-fluorobenzamide (**339A**):

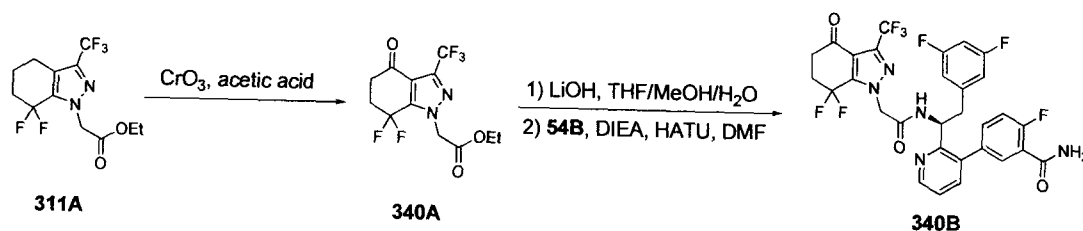
10 Compound 339A was prepared according to the method presented for the synthesis of Example 325 substituting Compound 79 for Compound 322 to afford the title compound. MS (m/z) 618.48 $[M+H]^+$.

Synthesis of (S)-5-(2-(2-(3,5-difluorophenyl)-1-(2-(3-(trifluoromethyl)-6,7-dihydro-1H-indazol-1-yl)acetamido)ethyl)pyridin-3-yl)-2-fluorobenzamide (**339B**):

15 Compound 339A (160 mg) was dissolved in 10 mL of toluene, to it was added 20 mg of p-toluenesulfonic acid. The reaction mixture was stirred at ambient temperature for 16 hours then was heated up to 100 °C for 2 hours. It was cooled down, and the solvent was removed. The residue was purified by silica gel chromatography eluting with EtOAc/Hexanes to afford 108 mg of the title compound. MS (m/z) 600.46 $[M+H]^+$. 1H NMR (400 MHz, $cdcl_3$) δ 8.50 (dd, $J = 4.7, 1.4$ Hz, 1H), 7.57 (dd, $J = 7.2, 2.1$ Hz, 1H), 7.49 – 7.29 (m, 2H), 7.17 (ddd, $J = 32.2, 13.6, 6.6$ Hz, 3H), 6.76 (d, $J = 9.0$ Hz, 1H), 6.51 – 6.34 (m, 2H), 6.08 (d, $J = 5.8$ Hz, 3H), 5.85 – 5.54 (m, 1H), 5.37 (dd, $J = 14.8, 7.9$ Hz, 1H), 4.67 (s, 2H), 2.94 – 2.73 (m, 2H), 2.72 – 2.56 (m, 2H), 2.48 – 2.31 (m, 2H).

25

Example 340



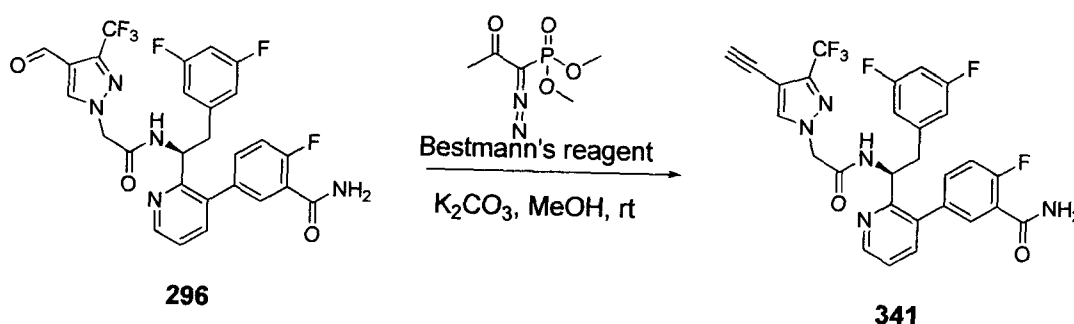
Synthesis of ethyl 2-(7,7-difluoro-4-oxo-3-(trifluoromethyl)-4,5,6,7-tetrahydro-1H-indazol-1-yl)acetate (**340A**):

Compound 340A was prepared according to the method presented for the synthesis of Example 285F substituting Compound 311A for Compound 285E to afford the title compound. MS (m/z) 326.96 [M+H]⁺.

Synthesis of (S)-5-(2-(1-(2-(7,7-difluoro-4-oxo-3-(trifluoromethyl)-4,5,6,7-tetrahydro-1H-indazol-1-yl)acetamido)-2-(3,5-difluorophenyl)ethyl)pyridin-3-yl)-2-fluorobenzamide (**340B**):

Compound 340B was prepared according to the method presented for the synthesis of Example 285G substituting Compound 340A for Compound 285F to afford 9 mg of the title compound. MS (m/z) 652.32 [M+H]⁺. ¹H NMR (400 MHz, cd₃od) δ 8.74 (dd, *J* = 4.9, 1.6 Hz, 1H), 7.70 (dd, *J* = 7.8, 1.6 Hz, 1H), 7.50 (dd, *J* = 7.8, 5.0 Hz, 1H), 7.41 (d, *J* = 4.9 Hz, 1H), 7.31 (s, 1H), 7.21 (dd, *J* = 10.7, 8.5 Hz, 1H), 6.67 (ddd, *J* = 9.3, 7.0, 2.3 Hz, 1H), 6.33 (d, *J* = 6.1 Hz, 2H), 5.37 (t, *J* = 7.6 Hz, 1H), 5.17 (s, 2H), 3.09 (d, *J* = 7.6 Hz, 2H), 2.84 – 2.61 (m, 4H).

Example 341

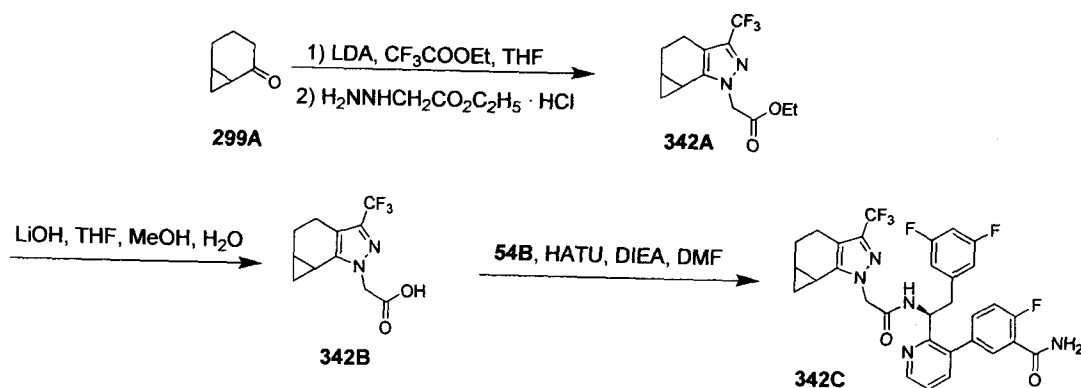


Synthesis of (S)-5-(2-(2-(3,5-difluorophenyl)-1-(2-(4-ethynyl-3-(trifluoromethyl)-1H-pyrazol-1-yl)acetamido)ethyl)pyridin-3-yl)-2-fluorobenzamide (**341**):

To a solution of Compound 296 (57 mg, 0.1 mmol) and dimethyl 1-diazo-2-oxopropylphosphonate (31 mg, 0.16 mmol) in MeOH (0.5 mL) was added K₂CO₃ (34.5 mg, 0.25 mmol). The resulting solution was stirred for 1 hour at ambient temperature. The reaction was then partitioned between EtOAc and 0.5 N HCl. The organic was dried over MgSO₄ and then concentrated. The crude was purified by reverse phase preparative HPLC to afford 22 mg of the product. MS (m/z) 572.29 [M+H]⁺. ¹H NMR (400 MHz, cd₃od) δ 8.70 (dd, *J* = 4.9, 1.6 Hz,

1H), 7.94 (s, 1H), 7.64 (dd, $J = 7.8, 1.6$ Hz, 1H), 7.52 – 7.40 (m, 2H), 7.33 (s, 1H), 7.22 (dd, $J = 10.7, 8.6$ Hz, 1H), 6.65 (t, $J = 9.1$ Hz, 1H), 6.30 (d, $J = 6.2$ Hz, 2H), 5.34 (t, $J = 7.5$ Hz, 1H), 4.94 (s, 2H), 3.60 (d, $J = 13.7$ Hz, 1H), 3.14 – 2.96 (m, 2H).

5 Example 342



- 10 Synthesis of ethyl 2-(3-(trifluoromethyl)-5,5a,6,6a-tetrahydrocyclopropa[g]indazol-1(4H)-yl)acetate (**342A**):

Compound 342 was prepared according to the method presented for the synthesis of Example 299B substituting ethyltrifluoroacetate for methyldifluoroacetate to afford the title compound. MS (m/z) 289.26 $[M+H]^+$.

15

Synthesis of 2-(3-(trifluoromethyl)-5,5a,6,6a-tetrahydrocyclopropa[g]indazol-1(4H)-yl)acetic acid (**342B**):

Compound 342B was prepared according to the method presented in the synthesis of Example 60G utilizing ethyl 2-(3-(trifluoromethyl)-5,5a,6,6a-tetrahydrocyclopropa[g]indazol-1(4H)-yl)acetate to afford the title compound. MS (m/z) 261.11 $[M+H]^+$.

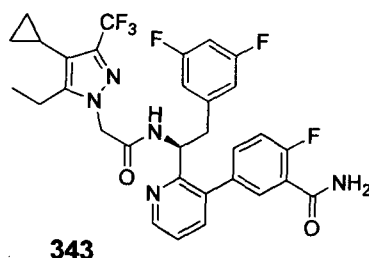
20

Synthesis of 5-(2-((1S)-2-(3,5-difluorophenyl)-1-(2-(3-(trifluoromethyl)-5,5a,6,6a-tetrahydrocyclopropa[g]indazol-1(4H)-yl)acetamido)ethyl)pyridin-3-yl)-2-fluorobenzamide (**342C**):

- 25 Compound 342C was prepared according to the method presented in the synthesis of Example 54 utilizing Compound 54B and 2-(3-(trifluoromethyl)-5,5a,6,6a-tetrahydrocyclopropa[g]indazol-1(4H)-yl)acetic acid to provide 68 mg of the title compound.

MS (m/z) 614.50 $[M+H]^+$. 1H NMR (400 MHz, cd_3od) δ 8.77 – 8.64 (m, 1H), 7.70 (t, $J = 6.7$ Hz, 1H), 7.47 (ddd, $J = 14.9, 7.6, 3.9$ Hz, 2H), 7.35 (s, 1H), 7.23 (dd, $J = 10.7, 8.5$ Hz, 1H), 6.68 (ddd, $J = 7.4, 6.0, 3.4$ Hz, 1H), 6.34 (dd, $J = 9.7, 7.4$ Hz, 2H), 5.38 (q, $J = 7.1$ Hz, 1H), 4.96 – 4.91 (m, 2H), 3.13 – 2.95 (m, 2H), 2.65 (d, $J = 18.0$ Hz, 1H), 2.25 – 1.98 (m, 2H), 1.94 – 1.52 (m, 3H), 0.96 (ddd, $J = 23.2, 8.3, 5.2$ Hz, 1H), 0.66 (td, $J = 10.1, 5.0$ Hz, 1H).

Example 343

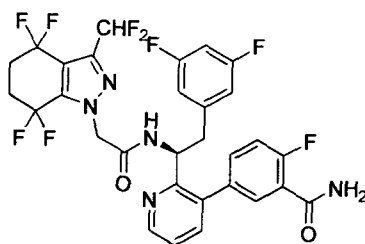


Synthesis of (S)-5-(2-(1-(2-(4-cyclopropyl-5-ethyl-3-(trifluoromethyl)-1H-pyrazol-1-yl)acetamido)-2-(3,5-difluorophenyl)ethyl)pyridin-3-yl)-2-fluorobenzamide (**343**):

Compound 343 was prepared according to the method presented for the synthesis of Example 276 substituting (S)-5-(2-(1-(2-(4-bromo-5-ethyl-3-(trifluoromethyl)-1H-pyrazol-1-yl)acetamido)-2-(3,5-difluorophenyl)ethyl)pyridin-3-yl)-2-fluorobenzamide (Compound 58) for

(S)-5-(2-(1-(2-(4-bromo-3-(trifluoromethyl)-1H-pyrazol-1-yl)acetamido)-2-(3,5-difluorophenyl)ethyl)pyridin-3-yl)-2-fluorobenzamide (Compound 463) to afford 10 mg of the title compound: MS (m/z) 616.36 $[M+H]^+$. 1H NMR (400 MHz, cd_3od) δ 8.70 (dd, $J = 4.9, 1.5$ Hz, 1H), 7.69 (dd, $J = 7.8, 1.6$ Hz, 1H), 7.53 – 7.40 (m, 2H), 7.35 (s, 1H), 7.22 (dd, $J = 10.7, 8.5$ Hz, 1H), 6.67 (t, $J = 9.2$ Hz, 1H), 6.33 (d, $J = 6.2$ Hz, 2H), 5.35 (t, $J = 7.6$ Hz, 1H), 4.84 (s, 2H), 3.05 (d, $J = 7.6$ Hz, 2H), 2.76 – 2.46 (m, 2H), 1.54 (dd, $J = 12.2, 6.8$ Hz, 1H), 1.07 (t, $J = 7.6$ Hz, 3H), 0.92 – 0.80 (m, 2H), 0.53 (q, $J = 5.7$ Hz, 2H).

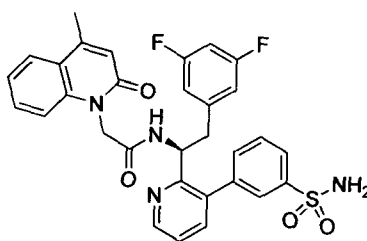
Example 344

**344**

Synthesis 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 (**344**):

- 5 Compound 344 was prepared according to the method presented in the synthesis of Example 54 utilizing Compound 54B and 2-(3-(difluoromethyl)-4,4,7,7-tetrafluoro-4,5,6,7-tetrahydro-1H-indazol-1-yl)acetic acid (Compound 287C) to provide 155 mg of the title compound. MS (m/z) 656.52 $[M+H]^+$. 1H NMR (400 MHz, cd_3od) δ 8.70 (dd, $J = 4.8, 1.6$ Hz, 1H), 7.62 (dd, $J = 7.8, 1.6$ Hz, 1H), 7.43 (dd, $J = 7.8, 4.9$ Hz, 1H), 7.37 (d, $J = 4.7$ Hz, 1H), 7.30 (bs, 1H), 7.21 (dd, $J =$
- 10 10.7, 8.5 Hz, 1H), 6.98 – 6.54 (m, 2H), 6.31 (d, $J = 6.3$ Hz, 2H), 5.34 (t, $J = 7.6$ Hz, 1H), 5.06 (s, 2H), 3.14 – 2.97 (m, 2H), 2.61 – 2.34 (m, 4H).

Example 345

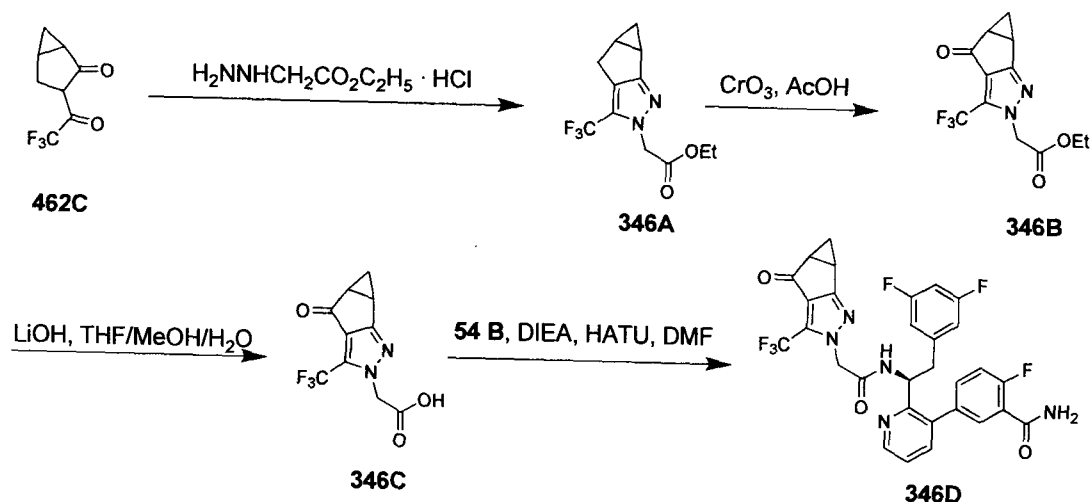
**345**

Synthesis of (S)-N-(2-(3,5-difluorophenyl)-1-(3-(3-sulfamoylphenyl)pyridin-2-yl)ethyl)-2-(4-methyl-2-oxoquinolin-1(2H)-yl)acetamide (**345**):

- Compound 345 was prepared according to the method presented in the synthesis of Example 55 utilizing Compound 55D and 2-(4-methyl-2-oxoquinolin-1(2H)-yl)acetic acid to afford (S)-N-(1-(3-bromopyridin-2-yl)-2-(3,5-difluorophenyl)ethyl)-2-(4-methyl-2-oxoquinolin-1(2H)-yl)acetamide, and then Suzuki coupling with 3-sulfamoylphenylboronic acid to provide 8 mg of the title compound. MS (m/z) 589.2 $[M+H]^+$. 1H NMR (400 MHz, cd_3od) δ 8.63 (d, $J = 4.5$ Hz, 1H), 7.78 (dd, $J = 20.9, 7.6$ Hz, 2H), 7.63 (s, 1H), 7.54 (d, $J = 7.8$ Hz, 1H), 7.44 (dd, $J = 14.9, 7.2$ Hz, 2H), 7.34 (dd, $J = 7.7, 4.7$ Hz, 1H), 7.22 (t, $J = 7.6$ Hz, 2H), 7.11 (d, $J = 8.5$ Hz, 1H),
- 20

6.58 (t, $J = 9.2$ Hz, 1H), 6.50 (s, 1H), 6.26 (d, $J = 6.2$ Hz, 2H), 5.31 (t, $J = 7.5$ Hz, 1H), 4.96 (s, 2H), 3.06 – 2.92 (m, 2H), 2.43 (d, $J = 5.0$ Hz, 3H).

Example 346



Synthesis of ethyl 2-(3-(trifluoromethyl)-4,4a,5,5a-tetrahydro-2H-cyclopropa[4,5]cyclopenta[1,2-c]pyrazol-2-yl)acetate (**346A**):

Compound 346A was prepared according to the method presented for the synthesis of

10 Compound 122D substituting 3-(2,2,2-trifluoroacetyl)bicyclo[3.1.0]hexan-2-one for Compound 122C afford the title compound: MS (m/z) 275.21 [$M+H$]⁺.

Synthesis of ethyl 2-(4-oxo-3-(trifluoromethyl)-4,4a,5,5a-tetrahydro-2H-cyclopropa[4,5]cyclopenta[1,2-c]pyrazol-2-yl)acetate (**346B**):

15 Compound 346B was prepared according to the method presented in the synthesis of Example 272A utilizing Compound 346A to provide the title compound. MS (m/z) 289.08 [$M+H$]⁺.

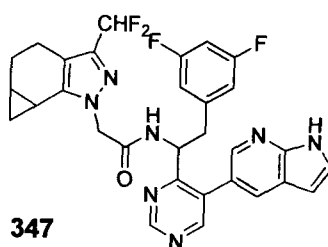
Synthesis of 2-(4-oxo-3-(trifluoromethyl)-4,4a,5,5a-tetrahydro-2H-cyclopropa[4,5]cyclopenta[1,2-c]pyrazol-2-yl)acetic acid (**346C**):

20 Compound 346C was prepared according to the method presented for the synthesis of Compound 60G substituting Compound 346B for Compound 60F to afford the title compound. MS (m/z) 261.08 [$M+H$]⁺.

Synthesis of 5-(2-((1S)-2-(3,5-difluorophenyl)-1-(2-(4-oxo-3-(trifluoromethyl)-4,4a,5,5a-tetrahydro-2H-cyclopropa[4,5]cyclopenta[1,2-c]pyrazol-2-yl)acetamido)ethyl)pyridin-3-yl)-2-fluorobenzamide (**346D**):

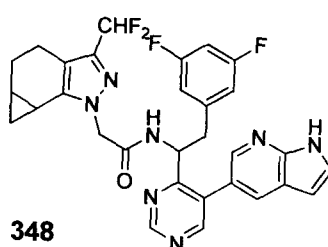
Compound 346D was prepared according to the method presented in the synthesis of Example 54 utilizing Compound 54B and Compound 346C to provide 16 mg of the title compound. MS (m/z) 614.18 $[M+H]^+$. 1H NMR (400 MHz, cd_3od) δ 8.71 (dd, $J = 4.9, 1.5$ Hz, 1H), 7.74 – 7.55 (m, 1H), 7.44 (ddd, $J = 12.7, 7.2, 4.8$ Hz, 2H), 7.32 (s, 1H), 7.22 (dd, $J = 14.2, 5.0$ Hz, 1H), 6.67 (t, $J = 9.2$ Hz, 1H), 6.33 (d, $J = 7.5$ Hz, 2H), 5.35 (t, $J = 7.5$ Hz, 1H), 4.99 (s, 2H), 3.17 – 3.00 (m, 2H), 2.81 (m, 1H), 2.61 (dt, $J = 8.7, 4.2$ Hz, 1H), 1.64 (dd, $J = 12.7, 8.1$ Hz, 1H), 1.54 – 1.44 (m, 1H).

Example 347



Compound 299D was purified by Chiral column chromatography using CHIRALPAK IC column eluting with Heptane:ethanol (80:20). The fastest eluent (1st peak) was collected, concentrated and high vacuum dried to provide 5 mg of the title compound as a mixture of diastereomers. MS (m/z) 576.07 $[M+H]^+$. 1H NMR (400 MHz, cd_3od) δ 9.20 (d, $J = 2.1$ Hz, 1H), 8.60 (s, 1H), 7.95 (s, 1H), 7.81 (d, $J = 1.9$ Hz, 1H), 7.46 (d, $J = 3.5$ Hz, 1H), 6.69 (ddd, $J = 11.3, 8.5, 1.9$ Hz, 1H), 6.61 – 6.42 (m, 2H), 6.31 (t, $J = 5.7$ Hz, 2H), 5.48 (td, $J = 7.4, 3.3$ Hz, 1H), 4.90 (d, $J = 17.7$ Hz, 2H), 3.13 – 2.87 (m, 2H), 2.70 (dd, $J = 15.6, 5.7$ Hz, 1H), 2.26 – 1.98 (m, 2H), 1.92 – 1.51 (m, 3H), 1.07 – 0.80 (m, 1H), 0.66 (d, $J = 6.6$ Hz, 1H).

Example 348

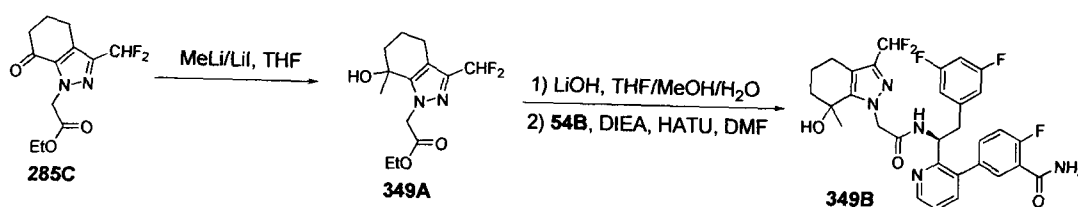


Compound 299D was purified by Chiral column chromatography using CHIRALPAK IC column eluting with Heptane:ethanol (80:20). The middle (2nd peak) was collected, concentrated and high vacuum dried to provide 10 mg of the title compound as a single

5 diastereomer. MS (*m/z*) 576.07 [*M*+*H*]⁺. ¹H NMR (400 MHz, *cd*₃od) δ 9.20 (s, 1H), 8.60 (s, 1H), 7.94 (d, *J* = 2.0 Hz, 1H), 7.81 (d, *J* = 1.9 Hz, 1H), 7.46 (d, *J* = 3.5 Hz, 1H), 6.69 (m, 1H), 6.52 (dd, *J* = 29.1, 25.6 Hz, 2H), 6.31 (d, *J* = 6.2 Hz, 2H), 5.47 (t, *J* = 7.4 Hz, 1H), 4.91 (s, 2H), 3.11 – 2.87 (m, 2H), 2.71 (dd, *J* = 15.7, 5.6 Hz, 1H), 2.32 – 1.96 (m, 2H), 1.76 (ddd, *J* = 75.6, 39.8, 26.6 Hz, 3H), 0.94 (m, 1H), 0.64 (dd, *J* = 10.4, 4.9 Hz, 1H).

10

Example 349



15 Synthesis of ethyl 2-(3-(difluoromethyl)-7-hydroxy-7-methyl-4,5,6,7-tetrahydro-1H-indazol-1-yl)acetate (**349A**):

Ethyl 2-(3-(difluoromethyl)-7-oxo-4,5,6,7-tetrahydro-1H-indazol-1-yl)acetate (Compound 285C, 100 mg, 0.37 mmol) was dissolved in 5 mL of THF and cooled down to 0 °C. To it was added a solution of methyllithium lithium iodide complex (1.0 M in diethyl ether, 1.8 mL, 1.8 mmol). After stirring at 0 °C for 5 min, It was quenched with NH₄Cl (sat'd aqueous solution) and extracted with EtOAc. The organic layer was separated, washed with brine, dried over MgSO₄, filtered and concentrated. The residue was purified by silica gel chromatography eluting with EtOAc/Hexanesto afford 27 mg of the title compound. MS (*m/z*) 288.03 [*M*+*H*]⁺.

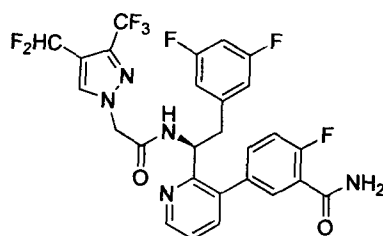
25 Synthesis of 5-(2-((1S)-1-(2-(3-(difluoromethyl)-7-hydroxy-7-methyl-4,5,6,7-tetrahydro-1H-indazol-1-yl)acetamido)-2-(3,5-difluorophenyl)ethyl)pyridin-3-yl)-2-fluorobenzamide (**349B**):

Compound 349B was prepared according to the method presented in the synthesis of Example 54 utilizing Compound 54B and 2-(3-(difluoromethyl)-7-hydroxy-7-methyl-4,5,6,7-tetrahydro-1H-indazol-1-yl)acetic acid to provide 31 mg of the title compound. MS (*m/z*) 614.02 [*M*+*H*]⁺. ¹H NMR (400 MHz, *cd*₃od) δ 8.74 – 8.64 (m, 1H), 7.78 – 7.59 (m, 1H), 7.53 – 7.41 (m, 2H), 7.33 (s, 1H), 7.27 – 7.17 (m, 1H), 6.84 – 6.40 (m, 2H), 6.31 (dd, *J* = 20.7, 6.1 Hz, 2H), 5.36 (dt,

30

$J = 15.4, 7.8$ Hz, 1H), 5.19 (m, 1H), 5.01 – 4.89 (m, 1H), 3.14 – 2.93 (m, 2H), 2.67 – 2.39 (m, 2H), 2.01 – 1.63 (m, 4H), 1.37 (d, $J = 5.3$ Hz, 3H).

Example 350



350

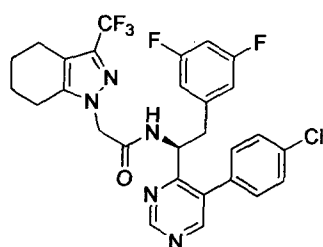
Synthesis of (S)-5-(2-(1-(2-(4-(difluoromethyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl)acetamido)-2-(3,5-difluorophenyl)ethyl)pyridin-3-yl)-2-fluorobenzamide (**350**):

Compound 350 was prepared according to the method presented for the synthesis of Example

10 150 substituting (S)-5-(2-(2-(3,5-difluorophenyl)-1-(2-(4-formyl-3-(trifluoromethyl)-1H-pyrazol-1-yl)acetamido)ethyl)pyridin-3-yl)-2-fluorobenzamide (Compound 296) for (S)-5-(2-(2-(3,5-difluorophenyl)-1-(2-(5-oxo-3-(trifluoromethyl)-4,5,6,7-tetrahydro-1H-indazol-1-yl)acetamido)ethyl)pyridin-3-yl)-2-fluorobenzamide (Compound 446) to afford 26 mg of the

15 title compound: MS (m/z) 598.10 $[M+H]^+$. 1H NMR (400 MHz, cd_3od) δ 8.71 (dd, $J = 4.9, 1.6$ Hz, 1H), 8.05 (s, 1H), 7.66 (dd, $J = 7.8, 1.6$ Hz, 1H), 7.55 – 7.38 (m, 2H), 7.34 (s, 1H), 7.22 (dd, $J = 10.7, 8.5$ Hz, 1H), 6.86 (t, $J = 55.2$ Hz, 1H), 6.66 (dd, $J = 10.4, 8.1$ Hz, 1H), 6.31 (d, $J = 6.2$ Hz, 2H), 5.35 (t, $J = 7.5$ Hz, 1H), 4.99 (s, 2H), 3.07 (d, $J = 7.6$ Hz, 2H).

Example 351



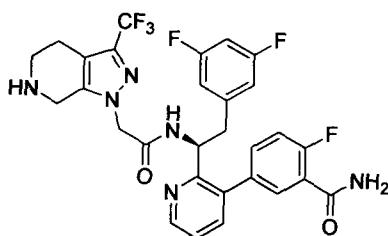
351

Synthesis of (S)-N-(1-(5-(4-chlorophenyl)pyrimidin-4-yl)-2-(3,5-difluorophenyl)ethyl)-2-(3-(trifluoromethyl)-4,5,6,7-tetrahydro-1H-indazol-1-yl)acetamide (**351**):

Compound 351 was prepared according to the method presented for the synthesis of Example 316 substituting 2-(3-(trifluoromethyl)-4,5,6,7-tetrahydro-1H-indazol-1-yl)acetic acid for 2-(5-hydroxy-1H-indol-3-yl)acetic acid to afford 20 mg of the title compound: MS (m/z) 576.1

[M+H]⁺. ¹H NMR (400 MHz, cd₃od) δ 9.22 (s, 1H), 8.55 (s, 1H), 7.44 (d, J = 8.1 Hz, 2H), 7.20 (d, J = 8.1 Hz, 2H), 6.74 (t, J = 9.1 Hz, 1H), 6.38 (d, J = 6.9 Hz, 2H), 5.45 (q, J = 7.1 Hz, 1H), 4.79 (s, 2H), 3.20 – 2.85 (m, 2H), 2.55 (t, J = 5.5 Hz, 2H), 2.51 – 2.31 (m, 2H), 1.85 – 1.65 (m, 4H).

Example 352



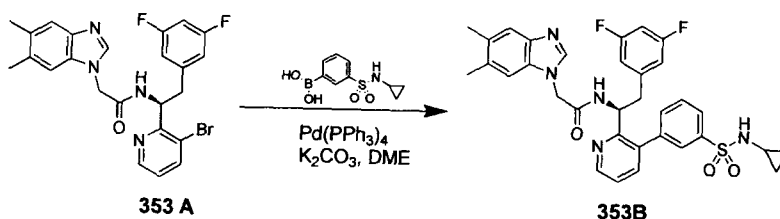
352

Synthesis of (S)-5-(2-(2-(3,5-difluorophenyl)-1-(2-(3-(trifluoromethyl)-4,5,6,7-tetrahydro-1H-pyrazolo[3,4-c]pyridin-1-yl)acetamido)ethyl)pyridin-3-yl)-2-fluorobenzamide (**352**):

Compound 352 was prepared according to the method presented in the synthesis of Example 303 utilizing Compound 378 to provide 10 mg of the title compound. MS (m/z) 603.13 [M+H]⁺.

¹H NMR (400 MHz, cd₃od) δ 8.70 (dd, J = 5.2, 1.5 Hz, 1H), 7.85 (d, J = 7.9 Hz, 1H), 7.61 (dd, J = 7.8, 5.2 Hz, 2H), 7.15 (d, J = 9.2 Hz, 2H), 6.63 (t, J = 9.2 Hz, 1H), 6.26 (d, J = 6.1 Hz, 2H), 5.29 (dd, J = 9.2, 6.1 Hz, 1H), 4.94 (s, 2H), 4.33 (s, 2H), 3.39 (t, J = 6.3 Hz, 2H), 3.10 (dd, J = 13.1, 6.3 Hz, 1H), 2.98 (dd, J = 13.2, 9.3 Hz, 1H), 2.86 (t, J = 6.0 Hz, 2H).

Example 353



Synthesis of (S)-N-(1-(3-bromopyridin-2-yl)-2-(3,5-difluorophenyl)ethyl)-2-(5,6-dimethyl-1H-benzo[d]imidazol-1-yl)acetamide (**353A**):

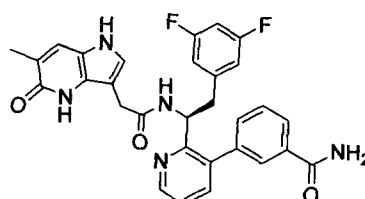
Compound 353 A was prepared according to the method presented in the synthesis of Example 55 utilizing Compound 55D and 2-(5,6-dimethyl-1H-benzo[d]imidazol-1-yl)acetic acid to provide the title compound. MS (m/z) 499.1 $[M+H]^+$.

5 Synthesis of (S)-N-(1-(3-(3-(N-cyclopropylsulfamoyl)phenyl)pyridin-2-yl)-2-(3,5-difluorophenyl)ethyl)-2-(5,6-dimethyl-1H-benzo[d]imidazol-1-yl)acetamide (**353B**):

Compound 353B was prepared according to the method presented in the synthesis of Example 55 utilizing 3-(N-cyclopropylsulfamoyl)phenylboronic acid to provide 5 mg of the title

10 compound. MS (m/z) 616.2 $[M+H]^+$. 1H NMR (400 MHz, cd_3od) δ 9.00 (s, 1H), 8.57 (d, $J = 4.7$ Hz, 1H), 7.67 (d, $J = 7.8$ Hz, 1H), 7.47 (dd, $J = 17.8, 9.1$ Hz, 2H), 7.39 (t, $J = 7.8$ Hz, 2H), 7.31 – 7.19 (m, 2H), 7.13 (d, $J = 7.6$ Hz, 1H), 6.48 (t, $J = 9.2$ Hz, 1H), 6.17 (d, $J = 6.4$ Hz, 2H), 5.15 (t, $J = 7.5$ Hz, 1H), 5.05 (s, 2H), 3.00 – 2.86 (m, 2H), 2.24 (d, $J = 5.9$ Hz, 6H), 1.98 – 1.77 (m, 1H), 0.40 – -0.11 (m, 4H).

15 Example 354

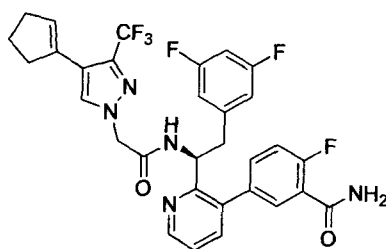


354

Synthesis of (S)-3-(2-(2-(3,5-difluorophenyl)-1-(2-(6-methyl-5-oxo-4,5-dihydro-1H-pyrrolo[3,2-b]pyridin-3-yl)acetamido)ethyl)pyridin-3-yl)benzamide (**354**):

20 Compound 354 was prepared according to the method presented for the synthesis of Example 331B utilizing Compound 360E to afford 5 mg of the title compound: MS (m/z) 542.1 $[M+H]^+$. 1H NMR (400 MHz, $cdcl_3$) δ 8.71 (m, 3H), 7.96 (d, $J = 7.8$ Hz, 2H), 7.88 (s, 1H), 7.74 (m, 2H), 7.56 – 7.48 (m, 1H), 7.41 (t, $J = 7.8$ Hz, 1H), 7.25 (s, 1H), 6.83 (d, $J = 7.7$ Hz, 1H), 6.44 (m, 2H), 6.01 (d, $J = 5.8$ Hz, 2H), 5.66 (dd, $J = 16.3, 8.9$ Hz, 1H), 3.70 (s, 2H), 3.09 – 2.78 (m, 2H),
25 2.25 (s, 3H).

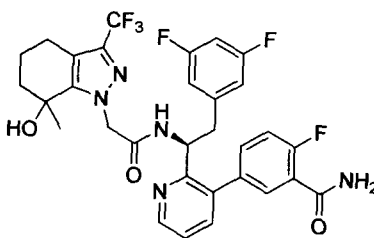
Example 355

**355**

Synthesis of (S)-5-(2-(1-(2-(4-cyclopentenyl-3-(trifluoromethyl)-1H-pyrazol-1-yl)acetamido)-2-(3,5-difluorophenyl)ethyl)pyridin-3-yl)-2-fluorobenzamide (**355**):

Compound 355 was prepared according to the method presented in the synthesis of Example 276 utilizing Compound 463 and cyclopentenylboronic acid to provide 19 mg of the title compound. MS (m/z) 614.35 $[M+H]^+$. 1H NMR (400 MHz, cd_3od) δ 8.69 (dd, $J = 4.9, 1.6$ Hz, 1H), 7.74 – 7.55 (m, 2H), 7.52 – 7.39 (m, 2H), 7.34 (s, 1H), 7.21 (dd, $J = 10.8, 8.5$ Hz, 1H), 6.65 (t, $J = 9.2$ Hz, 1H), 6.30 (d, $J = 6.3$ Hz, 2H), 5.96 (s, 1H), 5.35 (t, $J = 7.5$ Hz, 1H), 4.89 (s, 2H), 3.06 (d, $J = 7.6$ Hz, 2H), 2.59 (m, 2H), 2.47 (m, 2H), 2.06 – 1.82 (m, 2H).

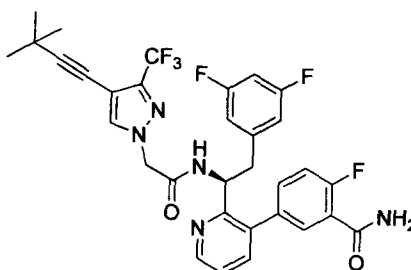
Example 356

**356**

Synthesis of 5-(2-((1S)-2-(3,5-difluorophenyl)-1-(2-(7-hydroxy-7-methyl-3-(trifluoromethyl)-4,5,6,7-tetrahydro-1H-indazol-1-yl)acetamido)ethyl)pyridin-3-yl)-2-fluorobenzamide (**356**):

Compound 356 was prepared according to the method presented in the synthesis of Example 349B utilizing Compound 272B to provide 24 mg of the title compound. MS (m/z) 631.96 $[M+H]^+$. 1H NMR (400 MHz, cd_3od) δ 8.62 – 8.49 (m, 1H), 7.47 (ddd, $J = 7.7, 4.4, 1.7$ Hz, 1H), 7.34 – 7.27 (m, 2H), 7.20 (s, 1H), 7.16 – 7.07 (m, 1H), 6.57 (t, $J = 9.3$ Hz, 1H), 6.21 (dd, $J = 24.2, 6.2$ Hz, 2H), 5.37 – 5.22 (m, 1H), 5.16 (dd, $J = 16.7, 4.3$ Hz, 1H), 4.90 (dd, $J = 16.6, 2.6$ Hz, 1H), 2.96 (td, $J = 13.0, 8.2$ Hz, 2H), 2.46 (m, 2H), 1.90 – 1.51 (m, 4H), 1.29 (d, $J = 2.1$ Hz, 3H).

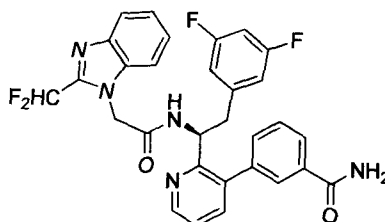
Example 357

**357**

Synthesis of (S)-5-(2-(2-(3,5-difluorophenyl)-1-(2-(4-(3,3-dimethylbut-1-ynyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl)acetamido)ethyl)pyridin-3-yl)-2-fluorobenzamide (**357**):

- 5 Compound **357** was prepared according to the method presented in the synthesis of Example 280 utilizing Compound 463 to provide 3 mg of the title compound. MS (m/z) 628.83 [M+H]⁺. ¹H NMR (400 MHz, cd₃od) δ 8.69 (dd, *J* = 4.8, 1.6 Hz, 1H), 7.76 (s, 1H), 7.59 (dd, *J* = 7.8, 1.6 Hz, 1H), 7.40 (dd, *J* = 7.8, 4.8 Hz, 2H), 7.31 (s, 1H), 7.21 (dd, *J* = 10.7, 8.6 Hz, 1H), 6.65 (t, *J* = 9.3 Hz, 1H), 6.29 (d, *J* = 6.4 Hz, 2H), 5.40 – 5.28 (m, 1H), 4.90 (s, 2H), 3.15 – 2.89 (m, 2H),
10 1.32 – 1.20 (m, 9H).

Example 358

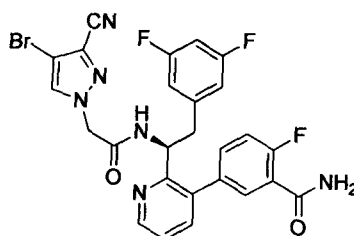
**358**

15 Synthesis of (S)-3-(2-(1-(2-(2-(difluoromethyl)-1H-benzo[d]imidazol-1-yl)acetamido)-2-(3,5-difluorophenyl)ethyl)pyridin-3-yl)benzamide (**358**):

- Compound **358** was prepared according to the method presented in the synthesis of Example 55 utilizing Compound 55D and 2-(2-(difluoromethyl)-1H-benzo[d]imidazol-1-yl)acetic acid, and
20 then Suzuki coupling with 3-carbamoylphenylboronic acid to afford 29 mg of the title compound. MS (m/z) 561.8 [M+H]⁺. ¹H NMR (400 MHz, cdcl₃) δ 10.08 (d, *J* = 7.7 Hz, 1H), 8.78 (d, *J* = 4.7 Hz, 1H), 8.12 – 7.96 (m, 2H), 7.93 – 7.69 (m, 3H), 7.53 (t, *J* = 7.7 Hz, 1H), 7.32 (m, 1H), 7.03 (m, 3H), 6.63 (t, *J* = 8.8 Hz, 1H), 6.15 (d, *J* = 5.7 Hz, 1H), 6.05 (s, 1H), 5.65 (dd, *J*

= 16.2, 8.7 Hz, 1H), 5.15 (dd, $J = 39.0, 17.2$ Hz, 2H), 3.17 (dd, $J = 13.4, 6.8$ Hz, 1H), 3.05 (dd, $J = 13.4, 9.6$ Hz, 1H).

Example 359

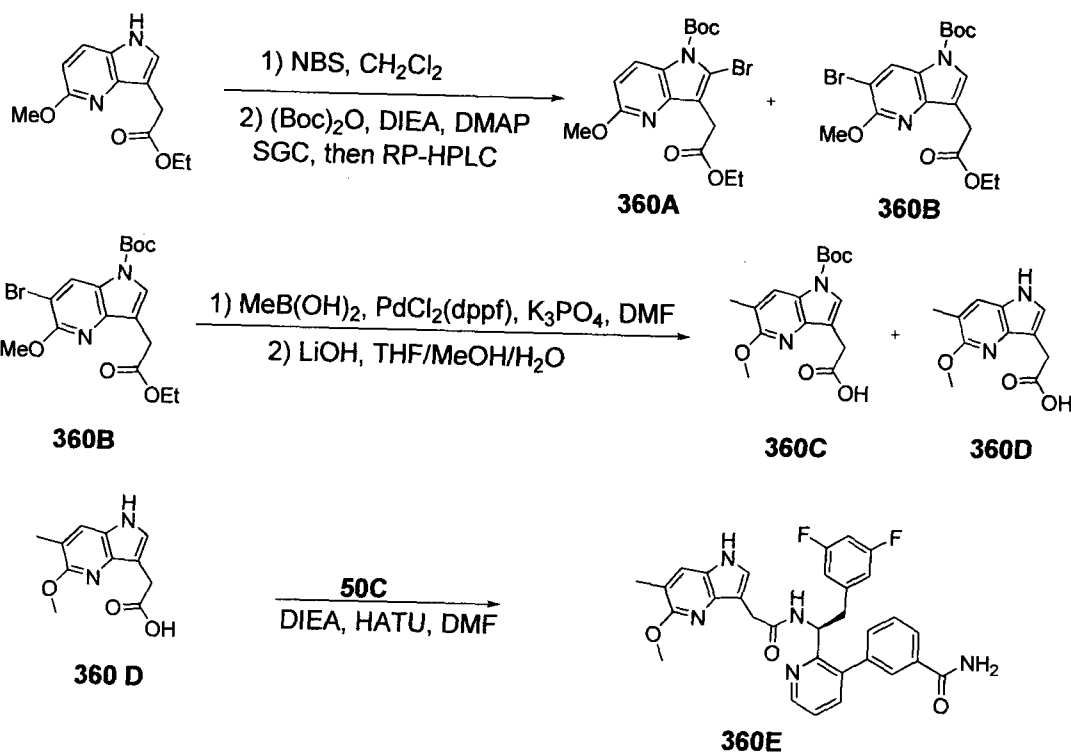


359

Synthesis of (S)-5-(2-(1-(2-(4-bromo-3-cyano-1H-pyrazol-1-yl)acetamido)-2-(3,5-difluorophenyl)ethyl)pyridin-3-yl)-2-fluorobenzamide (**359**):

Compound **359** was prepared according to the method presented in the synthesis of Example 56 utilizing Compound **56A** and 4-bromo-1H-pyrazole-3-carbonitrile to provide 6 mg of the title compound. MS (m/z) 585.03 $[M+H]^+$. ^1H NMR (400 MHz, cd_3od) δ 8.69 (dd, $J = 4.8, 1.6$ Hz, 1H), 7.92 (s, 1H), 7.55 (dd, $J = 7.8, 1.6$ Hz, 1H), 7.45 – 7.14 (m, 4H), 6.65 (t, $J = 9.2$ Hz, 1H), 6.30 (d, $J = 6.3$ Hz, 2H), 5.40 – 5.28 (m, 1H), 4.97 (s, 2H), 3.15 – 2.95 (m, 2H).

15 Example 360



Synthesis of tert-butyl 6-bromo-3-(2-ethoxy-2-oxoethyl)-5-methoxy-1H-pyrrolo[3,2-b]pyridine-1-carboxylate (**360B**):

Ethyl 2-(5-methoxy-1H-pyrrolo[3,2-b]pyridin-3-yl)acetate (1.0 g, 4.26 mmol) was dissolved in methylene chloride (40 mL) and cooled down to 0 °C with ice-water bath. NBS (760 mg, 4.26 mmol) was added in small portions over 1 hour. The reaction mixture was allowed to stir at 0 °C for two more hours. Then to it were added N,N-diisopropylethylamine (1.86 mL, 8.52 mmol), di-tert-butyl carbonate (1.86 G, 8.52 mmol) and 4-dimethylaminopyridine (52 mg, 0.42 mmol).

The resulting mixture was allowed to stir for overnight at ambient temperature. The reaction mixture was partitioned between methylene chloride and water. The organic layer was separated and dried over MgSO₄, filtered and the filtrate was concentrated to dryness. The residue was purified by silica gel chromatography eluting with EtOAc/hexanes, and then RP-HPLC eluting with acetonitrile/water to afford 455mg of **360A** and 131mg of the title compound. MS (*m/z*) 414.9 [M+H]⁺.

Synthesis of 2-(5-methoxy-6-methyl-1H-pyrrolo[3,2-b]pyridin-3-yl)acetic acid (**360D**):

Compound 360B (120 mg, 0.29 mmol) and methyl boronic acid (35 mg, 0.58 mmol) were dissolved in 3 mL of DMF. To it was added potassium phosphate tribasic (185 mg, 0.87 mmol). The system was degassed and purged with argon and then to it was added [1,1'-

bis(diphenylphosphino)ferrocene]dichloropalladium(II) (11 mg, 0.015 mmol). The mixture was heated up to 85 °C for 16 hours. After cooling down to ambient temperature the DMF solution was filtered and purified by RP HPLC eluting with acetonitrile and water to afford 28 mg of tert-butyl 3-(2-ethoxy-2-oxoethyl)-5-methoxy-6-methyl-1H-pyrrolo[3,2-b]pyridine-1-carboxylate and 38 mg of ethyl 2-(5-methoxy-6-methyl-1H-pyrrolo[3,2-b]pyridin-3-yl)acetate which was dissolved in 1.5 mL of THF/MeOH/H₂O (3/2/1), and to it was added LiOH.H₂O (30 mg). The reaction mixture was allowed to stir at ambient temperature for 20 min and purified by RP-HPLC eluting with acetonitrile and water to afford 15 mg of the title compound. MS (*m/z*) 221.2 [M+H]⁺.

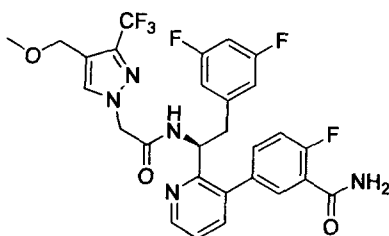
Synthesis of (S)-3-(2-(2-(3,5-difluorophenyl)-1-(2-(5-methoxy-6-methyl-1H-pyrrolo[3,2-b]pyridin-3-yl)acetamido)ethyl)pyridin-3-yl)benzamide (**360E**):

Compound 360E was prepared according to the method presented in the synthesis of Example 50 utilizing Compound 50C and 2-(5-methoxy-6-methyl-1H-pyrrolo[3,2-b]pyridin-3-yl)acetic

acid to provide 4 mg of the title compound. MS (m/z) 556.1 $[M+H]^+$. 1H NMR (400 MHz, $cdCl_3$) δ 9.77 (s, 1H), 8.81 (s, 1H), 8.62 (s, 1H), 7.93 (d, $J = 7.6$ Hz, 2H), 7.76 (s, 3H), 7.53 (s, 1H), 7.44 (t, $J = 7.8$ Hz, 1H), 7.23 (s, 1H), 6.96 (d, $J = 7.7$ Hz, 1H), 6.41 (d, $J = 9.5$ Hz, 2H), 6.02 (d, $J = 6.3$ Hz, 2H), 5.61 (d, $J = 8.1$ Hz, 1H), 4.08 (s, 3H), 3.76 (s, 2H), 2.94 (s, 2H), 2.23 (s, 3H).

5

Example 361



361

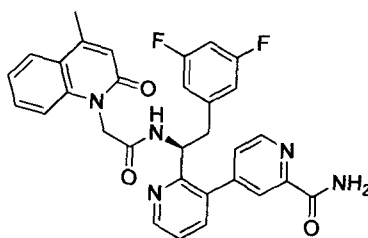
- 10 Synthesis of (S)-5-(2-(2-(3,5-difluorophenyl)-1-(2-(4-(methoxymethyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl)acetamido)ethyl)pyridin-3-yl)-2-fluorobenzamide (**361**):

Compound 296 (20 mg, 0.03 mmol) was dissolved in 1 mL of methanol and to it was added decaborane (8.5 mg, 0.06 mmol). The reaction mixture was stirred at ambient temperature for 3 days. It was quenched with $NaHCO_3$ (sat'd aqueous solution) and extracted with EtOAc. The organic layer was separated, washed with brine, dried over $MgSO_4$, filtered and concentrated.

- 15 The residue was purified by reverse phase HPLC eluting with acetonitrile/water (with 0.1% TFA) to afford 9.1 mg of the title compound. MS (m/z) 592.23 $[M+H]^+$. 1H NMR (400 MHz, cd_3od) δ 8.69 (dd, $J = 4.8, 1.6$ Hz, 1H), 7.74 (s, 1H), 7.64 (dd, $J = 7.8, 1.6$ Hz, 1H), 7.49 – 7.36 (m, 2H), 7.30 (bs, 1H), 7.21 (dd, $J = 10.7, 8.5$ Hz, 1H), 6.65 (dd, $J = 10.4, 8.1$ Hz, 1H), 6.30 (d, $J = 6.2$ Hz, 2H), 5.34 (t, $J = 7.5$ Hz, 1H), 4.92 (s, 2H), 4.39 (s, 2H), 3.33 (s, 2H), 3.12 – 3.00 (m, 2H).

20

Example 362

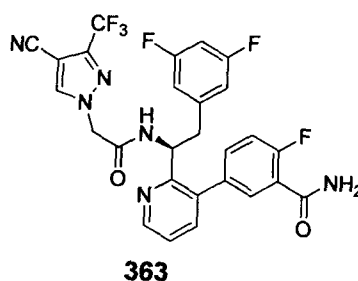


362

Synthesis of (S)-2-(2-(3,5-difluorophenyl)-1-(2-(4-methyl-2-oxoquinolin-1(2H)-yl)acetamido)ethyl)-3,4'-bipyridine-2'-carboxamide (**362**):

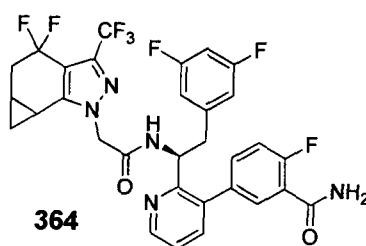
Compound **362** was prepared according to the method presented in the synthesis of Example 310 utilizing 2-(4-methyl-2-oxoquinolin-1(2H)-yl)acetic acid to provide 9 mg of the title compound. MS (m/z) 554.5 $[M+H]^+$. 1H NMR (400 MHz, cd_3od) δ 8.79 (d, J = 4.7 Hz, 1H), 8.59 (d, J = 5.0 Hz, 1H), 7.84 (d, J = 8.0 Hz, 1H), 7.73 – 7.61 (m, 2H), 7.51 (ddd, J = 12.7, 10.7, 5.1 Hz, 3H), 7.31 (t, J = 7.5 Hz, 1H), 7.21 (d, J = 8.5 Hz, 1H), 6.66 (t, J = 9.3 Hz, 1H), 6.59 (s, 1H), 6.32 (d, J = 6.4 Hz, 2H), 5.35 (t, J = 7.6 Hz, 1H), 5.07 (q, J = 16.7 Hz, 2H), 3.19 – 3.04 (m, 2H), 2.52 (s, 3H).

Example 363



Synthesis of (S)-5-(2-(1-(2-(4-cyano-3-(trifluoromethyl)-1H-pyrazol-1-yl)acetamido)-2-(3,5-difluorophenyl)ethyl)pyridin-3-yl)-2-fluorobenzamide (**363**):
 (S)-5-(2-(1-(2-(4-bromo-3-(trifluoromethyl)-1H-pyrazol-1-yl)acetamido)-2-(3,5-difluorophenyl)ethyl)pyridin-3-yl)-2-fluorobenzamide (Compound 463, 20 mg, 0.03 mmol) was dissolved in 0.5 mL of DMF. To it was added CuCN (5.7 mg, 0.06 mmol) and the reaction mixture was heated up to 200 °C for 16 hours. It was cooled down and 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 purified by reverse phase HPLC eluting with acetonitrile/water (with 0.1% TFA) to afford 6.5 mg of the title compound. MS (m/z) 573.22 $[M+H]^+$. 1H NMR (400 MHz, cd_3od) δ 8.70 (dd, J = 4.8, 1.6 Hz, 1H), 8.43 (s, 1H), 7.61 (dd, J = 7.8, 1.7 Hz, 1H), 7.42 (dd, J = 7.8, 4.9 Hz, 2H), 7.31 (s, 1H), 7.21 (dd, J = 10.7, 8.5 Hz, 1H), 6.65 (t, J = 9.2 Hz, 1H), 6.31 (d, J = 6.2 Hz, 2H), 5.41 – 5.23 (m, 1H), 5.04 (s, 2H), 3.09 (dd, J = 16.5, 9.7 Hz, 2H).

Example 364

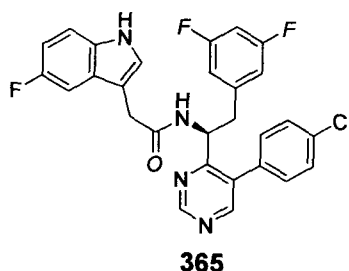


Synthesis of 5-(2-((1S)-1-(2-(4,4-difluoro-3-(trifluoromethyl)-5,5a,6,6a-tetrahydrocyclopropa[g]indazol-1(4H)-yl)acetamido)-2-(3,5-difluorophenyl)ethyl)pyridin-3-yl)-2-fluorobenzamide (**364**):

Compound **364** was prepared according to the method presented in the synthesis of Example 304 utilizing Compound **342A** to provide 2 mg of the title compound. MS (m/z) 650.00 $[M+H]^+$.

1H NMR (400 MHz, cd_3od) δ 8.78 – 8.62 (m, 1H), 7.58 (dd, J = 7.8, 1.7 Hz, 1H), 7.49 – 7.13 (m, 4H), 6.66 (d, J = 6.8 Hz, 1H), 6.34 (dd, J = 12.9, 6.6 Hz, 2H), 5.37 (t, J = 7.4 Hz, 1H), 5.11 – 4.92 (m, 2H), 3.07 (m, 2H), 2.63 (t, J = 16.6 Hz, 1H), 2.28 (m, 1H), 1.94-1.77 (m, 2H), 1.16 (m, 1H), 0.46 (m, 1H).

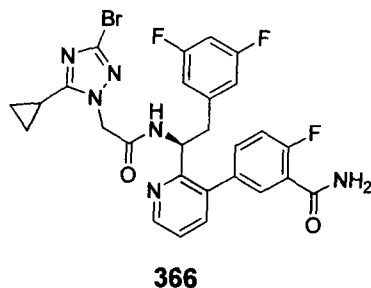
Example 365



Synthesis of (S)-N-(1-(5-(4-chlorophenyl)pyrimidin-4-yl)-2-(3,5-difluorophenyl)ethyl)-2-(5-fluoro-1H-indol-3-yl)acetamide (**365**):

Compound **365** was prepared according to the method presented for the synthesis of Example 279G substituting Compound **279D** and 2-(5-fluoro-1H-indol-3-yl)acetic acid for Compound **279E** and 2-(5,6-dimethyl-1H-benzo[d]imidazol-1-yl)acetic acid to afford 22 mg of the title compound: MS (m/z) 521.1 $[M+H]^+$. 1H NMR (400 MHz, cd_3od) δ 9.13 (s, 1H), 8.48 (s, 1H), 7.39 (d, J = 8.0 Hz, 2H), 7.28 (dd, J = 8.8, 4.3 Hz, 1H), 7.19 – 7.10 (m, 4H), 6.84 (t, J = 8.9 Hz, 1H), 6.68 (t, J = 9.2 Hz, 1H), 6.33 (d, J = 6.6 Hz, 2H), 5.42 (q, J = 7.1 Hz, 1H), 3.69 – 3.44 (m, 2H), 2.99 (d, J = 7.5 Hz, 2H).

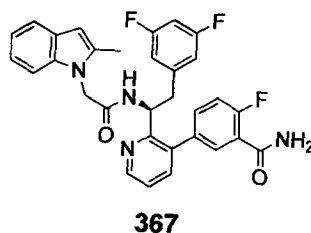
Example 366



Synthesis of (S)-5-(2-(1-(2-(3-bromo-5-cyclopropyl-1H-1,2,4-triazol-1-yl)acetamido)-2-(3,5-difluorophenyl)ethyl)pyridin-3-yl)-2-fluorobenzamide (**366**):

Compound **366** was prepared according to the method presented in the synthesis of Example 56 utilizing Compound 56A and 3-bromo-5-cyclopropyl-1H-1,2,4-triazole to provide 6 mg of the title compound. MS (m/z) 599.90 $[M+H]^+$. 1H NMR (400 MHz, cd_3od) δ 8.71 (dd, $J = 4.9, 1.6$ Hz, 1H), 7.66 (dd, $J = 7.8, 1.6$ Hz, 1H), 7.46 (dd, $J = 7.8, 4.9$ Hz, 2H), 7.33 (s, 1H), 7.23 (dd, $J = 10.7, 8.5$ Hz, 1H), 6.67 (dd, $J = 10.4, 8.0$ Hz, 1H), 6.34 (d, $J = 6.1$ Hz, 2H), 5.36 (t, $J = 7.6$ Hz, 1H), 4.97 (s, 2H), 3.08 (d, $J = 7.6$ Hz, 2H), 1.88 (m, 1H), 1.12 – 0.74 (m, 4H).

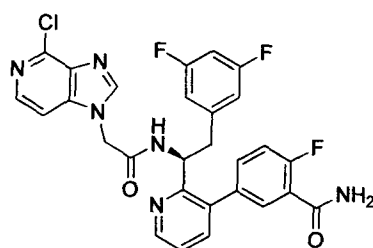
Example 367



Synthesis of (S)-5-(2-(2-(3,5-difluorophenyl)-1-(2-(2-methyl-1H-indol-1-yl)acetamido)ethyl)pyridin-3-yl)-2-fluorobenzamide (**367**):

Compound **367** was prepared according to the method presented in the synthesis of Example 54 utilizing Compound 54B and 3 2-(2-methyl-1H-indol-1-yl)acetic acid to provide 20 mg of the title compound. MS (m/z) 525.2 $[M+H]^+$. 1H NMR (400 MHz, cd_3od) δ 8.60 (d, $J = 4.8$ Hz, 1H), 7.88 (d, $J = 8.0$ Hz, 1H), 7.65 – 7.55 (m, 2H), 7.53 – 7.33 (m, 3H), 7.28 (d, $J = 7.8$ Hz, 1H), 7.12 (d, $J = 7.9$ Hz, 1H), 7.06 – 6.94 (m, 2H), 6.66 (t, $J = 9.2$ Hz, 1H), 6.25 (s, 3H), 5.46 (t, $J = 7.4$ Hz, 1H), 4.80 (s, 2H), 2.93 (qd, $J = 13.0, 7.3$ Hz, 2H), 2.30 (s, 3H).

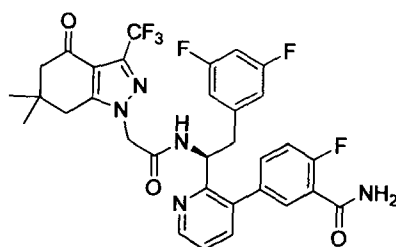
Example 368

**368**

Synthesis of (S)-5-(2-(1-(2-(4-chloro-1H-imidazo[4,5-c]pyridin-1-yl)acetamido)-2-(3,5-difluorophenyl)ethyl)pyridin-3-yl)-2-fluorobenzamide (**368**):

Compound **368** was prepared according to the method presented for the synthesis of Example 332 substituting 4-chloro-1H-imidazo[4,5-c]pyridine for 2-chloropyridin-4-ol to afford 6 mg of the title compound: MS (*m/z*) 565.60 [*M*+*H*]⁺. ¹H NMR (400 MHz, *cd*₃od) δ 8.65 (dd, *J* = 4.8, 1.6 Hz, 1H), 8.31 (s, 1H), 8.07 (t, *J* = 6.2 Hz, 1H), 7.65 – 7.49 (m, 1H), 7.50 – 7.35 (m, 3H), 7.22 (s, 1H), 7.12 (dd, *J* = 10.8, 8.5 Hz, 1H), 6.59 (dd, *J* = 10.4, 8.0 Hz, 1H), 6.28 (t, *J* = 9.0 Hz, 2H), 5.33 – 5.16 (m, 1H), 5.05 (s, 2H), 3.03 (m, 2H).

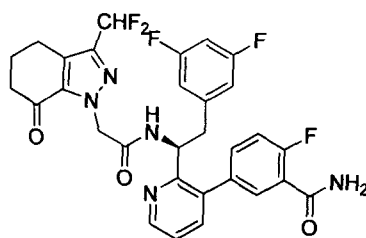
Example 369

**369**

Synthesis of (S)-5-(2-(2-(3,5-difluorophenyl)-1-(2-(6,6-dimethyl-4-oxo-3-(trifluoromethyl)-4,5,6,7-tetrahydro-1H-indazol-1-yl)acetamido)ethyl)pyridin-3-yl)-2-fluorobenzamide (**369**):

Compound **369** was prepared according to the method presented in the synthesis of Example 56 utilizing Compound 56A and 6,6-dimethyl-3-(trifluoromethyl)-6,7-dihydro-1H-indazol-4(5H)-one to provide 4 mg of the title compound. MS (*m/z*) 644.36 [*M*+*H*]⁺. ¹H NMR (400 MHz, *cd*₃od) δ 8.70 (d, *J* = 3.2 Hz, 1H), 7.56 (d, *J* = 6.1 Hz, 1H), 7.46-7.30 (m, 3H), 7.21 (d, *J* = 10.7 Hz, 1H), 6.66 (m, 1H), 6.35 (d, *J* = 6.0 Hz, 2H), 5.34 (m, 1H), 4.93 (s, 2H), 3.18 – 2.93 (m, 2H), 2.65 (s, 2H), 2.37 (s, 2H), 1.06 (d, *J* = 2.9 Hz, 6H).

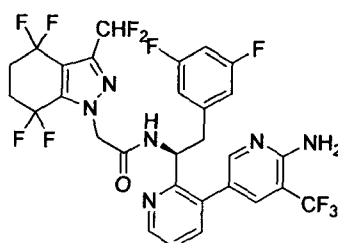
Example 370

**370**

Synthesis of (S)-5-(2-(1-(2-(3-(difluoromethyl)-7-oxo-4,5,6,7-tetrahydro-1H-indazol-1-yl)acetamido)-2-(3,5-difluorophenyl)ethyl)pyridin-3-yl)-2-fluorobenzamide (**370**):

- 5 Compound 370 was prepared according to the method presented in the synthesis of Example 54 utilizing Compound 54B and Compound 285C to provide 11 mg of the title compound. MS (m/z) 598.36 $[M+H]^+$. 1H NMR (400 MHz, cd_3od) δ 8.74 (dd, $J = 5.0, 1.6$ Hz, 1H), 7.72 (dd, $J = 7.8, 1.6$ Hz, 1H), 7.51 (dd, $J = 7.8, 5.0$ Hz, 1H), 7.45 – 7.26 (m, 2H), 7.20 (dd, $J = 10.7, 8.6$ Hz, 1H), 6.98 – 6.51 (m, 2H), 6.31 (d, $J = 6.1$ Hz, 2H), 5.35 (t, $J = 7.6$ Hz, 1H), 5.25 – 5.09 (m, 2H),
10 3.06 (dd, $J = 11.7, 10.1$ Hz, 2H), 2.87 (t, $J = 6.0$ Hz, 2H), 2.61 – 2.38 (m, 2H), 2.23 – 2.03 (m, 2H).

Example 371

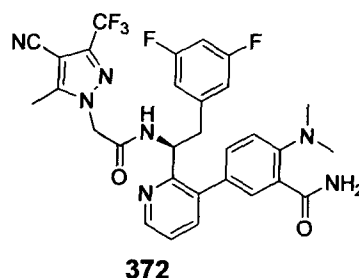
**371**

Synthesis of (S)-N-(1-(6'-amino-5'-(trifluoromethyl)-3,3'-bipyridin-2-yl)-2-(3,5-difluorophenyl)ethyl)-2-(3-(difluoromethyl)-4,4,7,7-tetrafluoro-4,5,6,7-tetrahydro-1H-indazol-1-yl)acetamide (**371**):

- 20 Compound 371 was prepared according to the method presented in the synthesis of Example 287E utilizing Compound 287D and 5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3-(trifluoromethyl)pyridin-2-amine to provide 15 mg of the title compound. MS (m/z) 679.35 $[M+H]^+$. 1H NMR (400 MHz, cd_3od) δ 8.74 (dd, $J = 4.8, 1.6$ Hz, 1H), 7.99 (s, 1H), 7.63 – 7.50

(m, 2H), 7.42 (dd, $J = 7.8, 4.8$ Hz, 1H), 7.03 – 6.56 (m, 2H), 6.37 (d, $J = 6.2$ Hz, 2H), 5.25 (t, $J = 7.6$ Hz, 1H), 5.16 – 4.94 (m, 2H), 3.12 (d, $J = 7.7$ Hz, 2H), 2.75 – 2.30 (m, 4H).

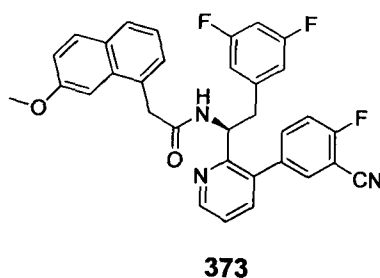
Example 372



Synthesis of (S)-5-(2-(1-(2-(4-cyano-5-methyl-3-(trifluoromethyl)-1H-pyrazol-1-yl)acetamido)-2-(3,5-difluorophenyl)ethyl)pyridin-3-yl)-2-(dimethylamino)benzamide (**372**):

Compound **372** was prepared according to the method presented in the synthesis of Example 363 utilizing Compound **275** to provide Compound **376** and 12 mg of the title compound as a side product. MS (m/z) 612.31 [$M+H$]⁺. ¹H NMR (400 MHz, cd_3cn) δ 8.76 (dd, $J = 4.8, 1.5$ Hz, 1H), 7.92 (s, 1H), 7.73 (d, $J = 8.4$ Hz, 1H), 7.64 (d, $J = 7.8$ Hz, 1H), 7.46 (dd, $J = 7.8, 4.8$ Hz, 1H), 7.33 (d, $J = 7.8$ Hz, 1H), 6.79 – 6.60 (m, 1H), 6.28 (d, $J = 6.5$ Hz, 2H), 5.53 (m, 1H), 5.07 – 4.83 (m, 2H), 3.18 (s, 6H), 3.02 (ddd, $J = 22.0, 13.0, 7.7$ Hz, 2H), 2.38 (s, 3H).

Example 373

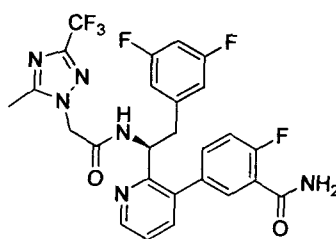


Synthesis of (S)-N-(1-(3-(3-cyano-4-fluorophenyl)pyridin-2-yl)-2-(3,5-difluorophenyl)ethyl)-2-(7-methoxynaphthalen-1-yl)acetamide (**373**):

Compound **373** was prepared according to the method presented in the synthesis of Example 55 utilizing Compound **55D** and 2-(7-methoxynaphthalen-1-yl)acetic acid to afford (S)-N-(1-(3-bromopyridin-2-yl)-2-(3,5-difluorophenyl)ethyl)-2-(7-methoxynaphthalen-1-yl)acetamide, and then Suzuki coupling with 3-cyano-4-fluorophenylboronic acid to provide 6 mg of the title

compound. MS (m/z) 552.2 $[M+H]^+$. 1H NMR (400 MHz, cd_3od) δ 8.64 (d, $J = 4.9$ Hz, 1H), 7.74 (dd, $J = 17.6, 8.5$ Hz, 2H), 7.58 (d, $J = 7.8$ Hz, 1H), 7.42 (dd, $J = 7.8, 4.9$ Hz, 2H), 7.34 (s, 1H), 7.32 – 7.24 (m, 3H), 7.21 (d, $J = 2.1$ Hz, 1H), 7.11 (dd, $J = 9.0, 2.4$ Hz, 1H), 6.70 (t, $J = 9.1$ Hz, 1H), 6.25 (d, $J = 6.3$ Hz, 2H), 5.35 – 5.16 (m, 1H), 3.98 (q, $J = 15.5$ Hz, 2H), 3.79 (s, 3H), 3.09 – 2.87 (m, 2H).

Example 374

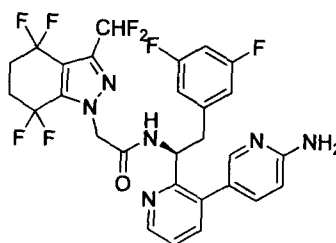


374

Synthesis of (S)-5-(2-(2-(3,5-difluorophenyl)-1-(2-(5-methyl-3-(trifluoromethyl)-1H-1,2,4-triazol-1-yl)acetamido)ethyl)pyridin-3-yl)-2-fluorobenzamide (**374**):

Compound **374** was prepared according to the method presented in the synthesis of Example 56 utilizing Compound 56A and 5-methyl-3-(trifluoromethyl)-1H-1,2,4-triazole to provide 40 mg of the title compound. MS (m/z) 563.32 $[M+H]^+$. 1H NMR (400 MHz, cd_3od) δ 8.72 (dd, $J = 4.9, 1.5$ Hz, 1H), 7.67 (dd, $J = 7.8, 1.6$ Hz, 1H), 7.47 (dd, $J = 7.8, 4.9$ Hz, 2H), 7.32 (s, 1H), 7.22 (dd, $J = 10.7, 8.6$ Hz, 1H), 6.78 – 6.49 (m, 1H), 6.34 (d, $J = 6.2$ Hz, 2H), 5.36 (t, $J = 7.6$ Hz, 1H), 5.02 (d, $J = 17.1$ Hz, 2H), 3.09 (d, $J = 7.6$ Hz, 2H), 2.39 (s, 3H).

20 Example 375

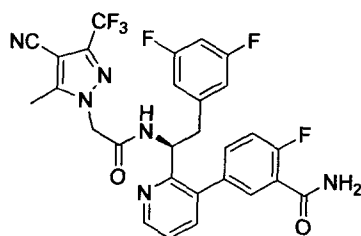


375

Synthesis of (S)-N-(1-(6'-amino-3,3'-bipyridin-2-yl)-2-(3,5-difluorophenyl)ethyl)-2-(3-(difluoromethyl)-4,4,7,7-tetrafluoro-4,5,6,7-tetrahydro-1H-indazol-1-yl)acetamide (**375**):

Compound 375 was prepared according to the method presented in the synthesis of Example 287E utilizing 287D and 5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pyridin-2-amine to provide 11 mg of the title compound. MS (m/z) 611.34 $[M+H]^+$. 1H NMR (400 MHz, cd_3od) δ 8.74 (dd, $J = 4.7, 1.6$ Hz, 1H), 7.64 – 7.50 (m, 3H), 7.39 (dd, $J = 7.8, 4.8$ Hz, 1H), 7.03 – 6.88 (m, 1H), 6.81 – 6.61 (m, 2H), 6.42 (d, $J = 6.3$ Hz, 2H), 5.27 (t, $J = 7.6$ Hz, 1H), 5.14 – 4.99 (m, 2H), 3.12 (d, $J = 7.7$ Hz, 2H), 2.70 – 2.34 (m, 4H).

Example 376



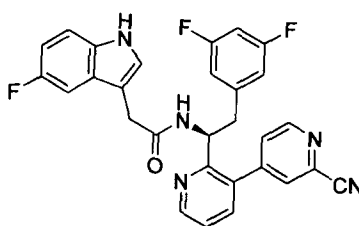
376

Synthesis of (S)-5-(2-(1-(2-(4-cyano-5-methyl-3-(trifluoromethyl)-1H-pyrazol-1-yl)acetamido)-2-(3,5-difluorophenyl)ethyl)pyridin-3-yl)-2-fluorobenzamide (**376**):

Compound 376 was prepared according to the method presented in the synthesis of Example 363 utilizing Compound 275 to provide 7 mg of the title compound. MS (m/z) 587.28 $[M+H]^+$.

1H NMR (400 MHz, cd_3od) δ 8.71 (dd, $J = 4.9, 1.6$ Hz, 1H), 7.65 (dd, $J = 7.8, 1.6$ Hz, 1H), 7.45 (dd, $J = 7.8, 4.9$ Hz, 2H), 7.32 (s, 1H), 7.22 (dd, $J = 10.7, 8.6$ Hz, 1H), 6.67 (t, $J = 9.2$ Hz, 1H), 6.33 (d, $J = 6.2$ Hz, 2H), 5.35 (t, $J = 7.6$ Hz, 1H), 4.99 (s, 2H), 3.08 (d, $J = 7.7$ Hz, 2H), 2.36 (s, 3H).

Example 377

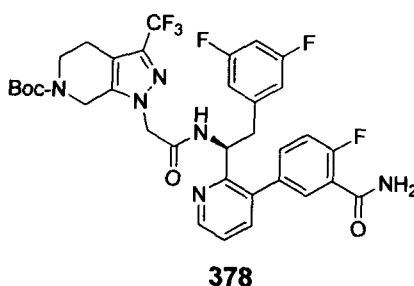


377

Synthesis of (S)-N-(1-(2'-cyano-3,4'-bipyridin-2-yl)-2-(3,5-difluorophenyl)ethyl)-2-(5-fluoro-1H-indol-3-yl)acetamide (**377**):

Compound 377 was prepared according to the method presented in the synthesis of Example 55 utilizing Compound 55E and 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)picolinonitrile to provide 5 mg of the title compound. MS (m/z) 512.1 $[M+H]^+$. 1H NMR (400 MHz, $cdCl_3$) δ 8.83 (d, $J = 5.0$ Hz, 1H), 8.62 (d, $J = 4.2$ Hz, 1H), 8.24 (s, 1H), 8.09 (d, $J = 7.1$ Hz, 1H), 7.91 – 7.79 (m, 1H), 7.69 (m, 2H), 7.30 (m, 1H), 7.22 (d, $J = 2.2$ Hz, 1H), 6.94 (m, 1H), 6.84 (dd, $J = 9.4$, 2.3 Hz, 1H), 6.69 (t, $J = 8.7$ Hz, 1H), 6.11 (m, 2H), 5.36 – 5.12 (m, 1H), 3.70 (q, $J = 16.3$ Hz, 2H), 3.06 (dd, $J = 13.5$, 6.3 Hz, 1H), 2.94 (dd, $J = 13.4$, 9.9 Hz, 1H).

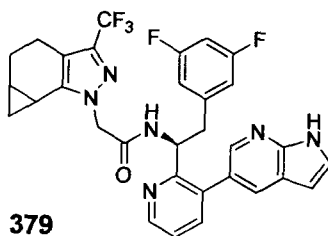
Example 378



Synthesis of (S)-tert-butyl 1-(2-(1-(3-(3-carbamoyl-4-fluorophenyl)pyridin-2-yl)-2-(3,5-difluorophenyl)ethylamino)-2-oxoethyl)-3-(trifluoromethyl)-4,5-dihydro-1H-pyrazolo[3,4-c]pyridine-6(7H)-carboxylate (**378**):

Compound 378 was prepared according to the method presented in the synthesis of Example 56 utilizing 56A and tert-butyl 3-(trifluoromethyl)-4,5-dihydro-1H-pyrazolo[3,4-c]pyridine-6(7H)-carboxylate to provide 6 mg of the title compound. MS (m/z) 703.14 $[M+H]^+$. 1H NMR (400 MHz, cd_3od) δ 8.69 (d, $J = 4.8$ Hz, 1H), 7.64 – 7.50 (m, 1H), 7.37 (m, 3H), 7.25 – 7.15 (m, 1H), 6.64 (m, 1H), 6.30 (d, $J = 6.3$ Hz, 2H), 5.33 (m, 1H), 4.85 (s, 2H), 4.46 (s, 2H), 3.18 – 2.93 (m, 4H), 2.63 (m, 2H), 1.45 (s, 9H).

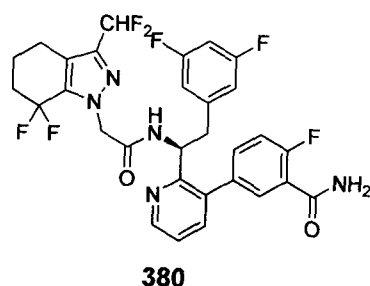
Example 379



Synthesis of N-((S)-1-(3-(1H-pyrrolo[2,3-b]pyridin-5-yl)pyridin-2-yl)-2-(3,5-difluorophenyl)ethyl)-2-(3-(trifluoromethyl)-5,5a,6,6a-tetrahydrocyclopropa[g]indazol-1(4H)-yl)acetamide (**379**):

Compound 379 was prepared according to the method presented in the synthesis of Example 61F utilizing Compound 342B and Compound 61E to provide 19 mg of the title compound. MS (m/z) 593.42 $[M+H]^+$. 1H NMR (400 MHz, cd_3od) δ 8.86 – 8.64 (m, 1H), 8.09 (s, 1H), 7.96 (m, 1H), 7.70 (m, 1H), 7.63 (d, $J = 3.5$ Hz, 1H), 7.54 – 7.38 (m, 1H), 6.81 – 6.58 (m, 2H), 6.30 (m, 2H), 5.33 (m, 1H), 4.93 (m, 2H), 3.23 – 2.96 (m, 2H), 2.65 (m, 1H), 2.15 (m, 2H), 1.88 – 1.47 (m, 3H), 1.09 – 0.76 (m, 1H), 0.66 (m, 1H).

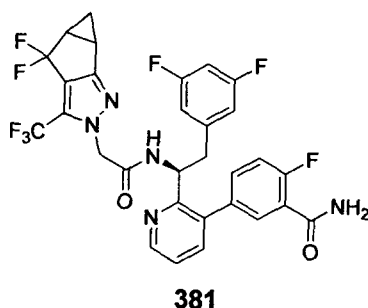
Example 380



Synthesis of (S)-5-(2-(1-(2-(3-(difluoromethyl)-7,7-difluoro-4,5,6,7-tetrahydro-1H-indazol-1-yl)acetamido)-2-(3,5-difluorophenyl)ethyl)pyridin-3-yl)-2-fluorobenzamide (**380**):

Compound 380 was prepared according to the method presented in the synthesis of Example 54 utilizing Compound 54B and Compound 285E to provide 40 mg of the title compound. MS (m/z) 620.40 $[M+H]^+$. 1H NMR (400 MHz, cd_3od) δ 8.71 (dd, $J = 5.0, 1.6$ Hz, 1H), 7.71 (dd, $J = 7.8, 1.6$ Hz, 1H), 7.50 (dd, $J = 7.8, 5.0$ Hz, 1H), 7.44 – 7.28 (m, 2H), 7.22 (dd, $J = 10.7, 8.5$ Hz, 1H), 6.94 – 6.53 (m, 2H), 6.32 (m, 2H), 5.35 (t, $J = 7.6$ Hz, 1H), 5.01 (m, 2H), 3.05 (d, $J = 7.6$ Hz, 2H), 2.67 (m, 2H), 2.35 – 2.04 (m, 2H), 2.05 – 1.80 (m, 2H).

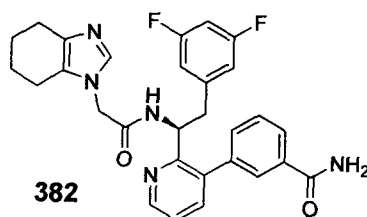
Example 381



Synthesis of 5-(2-((1S)-1-(2-(4,4-difluoro-3-(trifluoromethyl)-4,4a,5,5a-tetrahydro-2H-cyclopropa[4,5]cyclopenta[1,2-c]pyrazol-2-yl)acetamido)-2-(3,5-difluorophenyl)ethyl)pyridin-3-yl)-2-fluorobenzamide (**381**):

- 5 Compound 381 was prepared according to the method presented in the synthesis of Example 304 utilizing Compound 346B to provide 41 mg of the title compound. MS (m/z) 636.38 $[M+H]^+$. 1H NMR (400 MHz, cd_3od) δ 8.71 (dd, $J = 4.9, 1.6$ Hz, 1H), 7.74 – 7.60 (m, 1H), 7.49 – 7.29 (m, 3H), 7.27 – 7.15 (m, 1H), 6.67 (t, $J = 9.2$ Hz, 1H), 6.32 (d, $J = 8.1$ Hz, 2H), 5.35 (t, $J = 7.5$ Hz, 1H), 4.94 (s, 2H), 3.05 (d, $J = 7.6$ Hz, 2H), 2.72 – 2.41 (m, 2H), 1.41 (dd, $J = 14.1, 7.6$ Hz, 1H), 1.06 (m, 1H).

Example 382

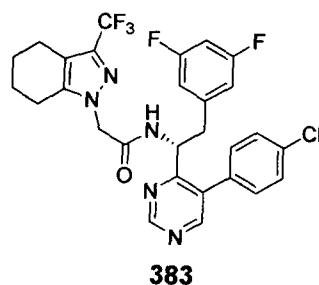


15

Synthesis of (S)-3-(2-(2-(3,5-difluorophenyl)-1-(2-(4,5,6,7-tetrahydro-1H-benzo[d]imidazol-1-yl)acetamido)ethyl)pyridin-3-yl)benzamide (**382**):

- Compound 382 was prepared according to the method presented in the synthesis of Example 56 utilizing Compound 286 and 3-carbamoylphenylboronic acid to provide 8 mg of the title compound. MS (m/z) 516.2 $[M+H]^+$. 1H NMR (400 MHz, $cdcl_3$) δ 9.97 (d, $J = 8.3$ Hz, 1H), 8.67 (m, 2H), 7.98 – 7.71 (m, 3H), 7.61 (m, 1H), 7.46 – 7.21 (m, 2H), 6.92 (m, 1H), 6.51 (t, $J = 8.8$ Hz, 2H), 6.13 (d, $J = 6.0$ Hz, 2H), 5.53 (d, $J = 8.2$ Hz, 1H), 4.78 (m, 2H), 3.15 – 2.86 (m, 2H), 2.51 (m, 2H), 2.30 (m, 2H), 1.73 (m, 4H).

25 Example 383

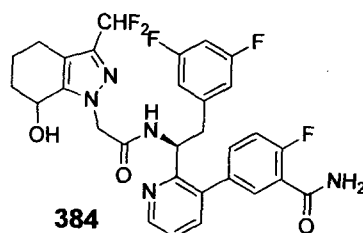


Synthesis (R)-N-(1-(5-(4-chlorophenyl)pyrimidin-4-yl)-2-(3,5-difluorophenyl)ethyl)-2-(3-(trifluoromethyl)-4,5,6,7-tetrahydro-1H-indazol-1-yl)acetamide(**383**):

Compound 383 was prepared according to the method presented for the synthesis of Example 279G substituting 2-(3-(trifluoromethyl)-4,5,6,7-tetrahydro-1H-indazol-1-yl)acetic acid for 2-

(5,6-dimethyl-1H-benzo[d]imidazol-1-yl)acetic acid to afford 20 mg of the title compound: MS (m/z) 576.1 $[M+H]^+$. 1H NMR (400 MHz, $cdCl_3$) δ 9.17 (s, 1H), 8.57 (s, 1H), 7.48 (m, 3H), 7.09 (d, $J = 8.2$ Hz, 2H), 6.60 (t, $J = 8.8$ Hz, 1H), 6.17 (d, $J = 6.1$ Hz, 2H), 5.53 (dd, $J = 15.1, 7.5$ Hz, 1H), 4.72 (s, 2H), 2.83 (d, $J = 7.2$ Hz, 2H), 2.68 – 2.42 (m, 4H), 1.80 (dd, $J = 26.2, 5.4$ Hz, 4H).

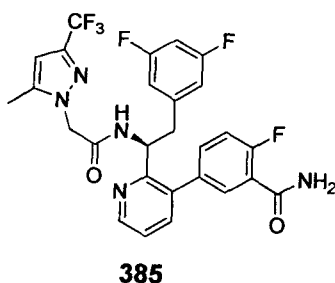
10 Example 384



Synthesis of 5-(2-(((1S)-1-(2-(3-(difluoromethyl)-7-hydroxy-4,5,6,7-tetrahydro-1H-indazol-1-yl)acetamido)-2-(3,5-difluorophenyl)ethyl)pyridin-3-yl)-2-fluorobenzamide (**384**):

15 Compound 384 was prepared according to the method presented for the synthesis of Example 325 utilizing Compound 370 to afford 15 mg of the title compound. MS (m/z) 600.20 $[M+H]^+$. 1H NMR (400 MHz, cd_3od) δ 8.70 (d, $J = 5.0$ Hz, 1H), 7.71 (td, $J = 8.5, 1.6$ Hz, 1H), 7.49 (m, 2H), 7.34 (s, 1H), 7.22 (m, 1H), 6.81 – 6.47 (m, 2H), 6.31 (dd, $J = 9.5, 7.3$ Hz, 2H), 5.47 – 5.20 (m, 1H), 5.07 – 4.86 (m, 2H), 4.70 (m, 1H), 3.12 – 2.95 (m, 2H), 2.82 – 2.26 (m, 2H), 1.99 – 1.55 (m, 4H).

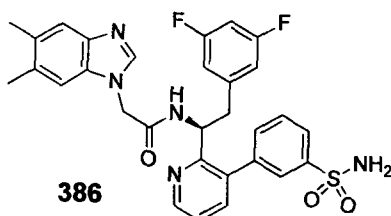
Example 385



Synthesis of (S)-5-(2-(2-(3,5-difluorophenyl)-1-(2-(5-methyl-3-(trifluoromethyl)-1H-pyrazol-1-yl)acetamido)ethyl)pyridin-3-yl)-2-fluorobenzamide (**385**):

Compound **385** was prepared according to the method presented in the synthesis of Example 56 utilizing Compound 56A and 5-methyl-3-(trifluoromethyl)-1H-pyrazole to provide 33 mg of the title compound. MS (m/z) 599.90 $[M+H]^+$. 1H NMR (400 MHz, cd_3od) δ 8.71 (dd, $J = 4.9, 1.6$ Hz, 1H), 7.68 (dd, $J = 7.8, 1.6$ Hz, 1H), 7.54 – 7.43 (m, 2H), 7.34 (s, 1H), 7.22 (dd, $J = 10.7, 8.5$ Hz, 1H), 6.67 (tt, $J = 9.2, 2.3$ Hz, 1H), 6.43 – 6.18 (m, 3H), 5.37 (t, $J = 7.5$ Hz, 1H), 4.88 (s, 2H), 3.07 (d, $J = 7.6$ Hz, 2H), 2.20 (s, 3H).

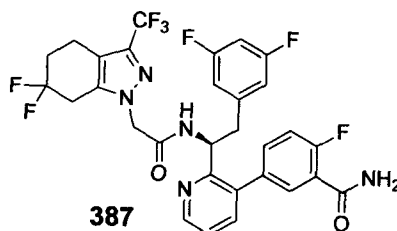
10 Example 386



Synthesis of (S)-N-(2-(3,5-difluorophenyl)-1-(3-(3-sulfamoylphenyl)pyridin-2-yl)ethyl)-2-(5,6-dimethyl-1H-benzo[d]imidazol-1-yl)acetamide(**386**):

15 Compound **386** was prepared according to the method presented in the synthesis of Example 353 substituting 3-sulfamoylphenylboronic acid for 3-(N-cyclopropylsulfamoyl)phenylboronic acid to provide 10 mg of the title compound. MS (m/z) 616.2 $[M+H]^+$. 1H NMR (400 MHz, cd_3od) δ 9.23 (s, 1H), 8.77 (d, $J = 4.8$ Hz, 1H), 7.90 (d, $J = 8.0$ Hz, 1H), 7.76 – 7.51 (m, 4H), 7.49 – 7.38 (m, 2H), 7.29 (d, $J = 7.8$ Hz, 1H), 6.66 (t, $J = 9.2$ Hz, 1H), 6.36 (d, $J = 6.5$ Hz, 2H),
20 5.37 (t, $J = 7.6$ Hz, 1H), 5.27 (s, 2H), 3.15 (m, 2H), 2.45 (d, $J = 3.0$ Hz, 6H).

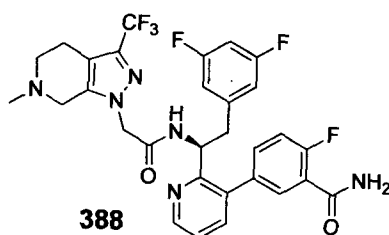
Example 387



25 Synthesis of (S)-5-(2-(1-(2-(6,6-difluoro-3-(trifluoromethyl)-4,5,6,7-tetrahydro-1H-indazol-1-yl)acetamido)-2-(3,5-difluorophenyl)ethyl)pyridin-3-yl)-2-fluorobenzamide(**387**):

Compound 387 was prepared according to the method presented in the synthesis of Example 150 utilizing Compound 322 to provide 2 mg of the title compound. MS (m/z) 638.06 $[M+H]^+$. 1H NMR (400 MHz, cd_3od) δ 8.70 (dd, $J = 4.9, 1.6$ Hz, 1H), 7.74 – 7.61 (m, 1H), 7.46 (m, 2H), 7.35 (s, 1H), 7.22 (m, 1H), 6.72 – 6.56 (m, 1H), 6.34 (d, $J = 6.2$ Hz, 2H), 5.36 (t, $J = 7.6$ Hz, 1H), 4.84 (s, 2H), 3.15 – 2.96 (m, 4H), 2.75 (t, $J = 6.5$ Hz, 2H), 2.20 (tt, $J = 13.4, 6.5$ Hz, 2H).

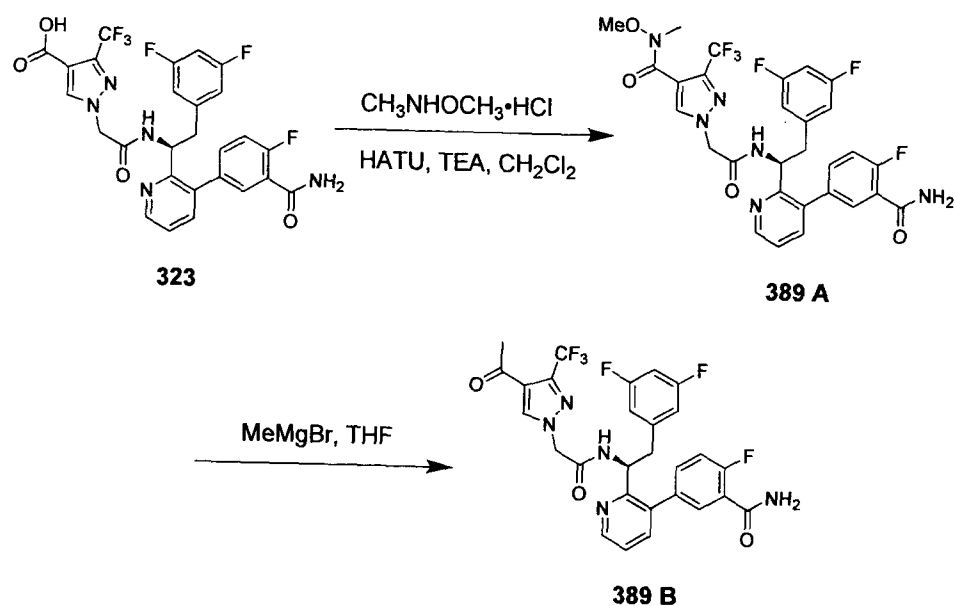
Example 388



Synthesis of (S)-5-(2-(2-(3,5-difluorophenyl)-1-(2-(6-methyl-3-(trifluoromethyl)-4,5,6,7-tetrahydro-1H-pyrazolo[3,4-c]pyridin-1-yl)acetamido)ethyl)pyridin-3-yl)-2-fluorobenzamide (**388**):

Compound 388 was prepared according to the method presented in the synthesis of Example 324 utilizing Compound 352 to provide 22 mg of the title compound. MS (m/z) 617.37 $[M+H]^+$. 1H NMR (400 MHz, cd_3od) δ 8.71 (dd, $J = 4.8, 1.3$ Hz, 1H), 7.61 (m, 2H), 7.49 – 7.33 (m, 1H), 7.30 – 6.98 (m, 2H), 6.77 – 6.52 (m, 1H), 6.31 (d, $J = 6.2$ Hz, 2H), 5.31 (m, 1H), 5.00 – 4.89 (m, 2H), 4.48 (bs, 2H), 3.58 (bs, 2H), 3.23 – 2.93 (m, 7H).

Example 389



Synthesis of (S)-1-(2-(1-(3-(3-carbamoyl-4-fluorophenyl)pyridin-2-yl)-2-(3,5-difluorophenyl)ethylamino)-2-oxoethyl)-N-methoxy-N-methyl-3-(trifluoromethyl)-1H-pyrazole-4-carboxamide (**389A**):

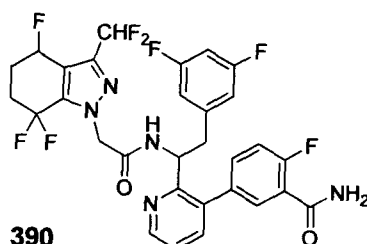
To a mixture of Compound 323 (222 mg, 0.38 mmol) and N,O-dimethylhydroxylamine hydrochloride (73 mg, 0.75 mmol) were added triethylamine (159 μ L, 1.1 mmol) and HATU (217 mg, 0.57 mmol). The reaction was allowed to stir at ambient temperature for 1 hour, and then partitioned between CH_2Cl_2 and 5% LiCl aqueous solution. The organic layer was separated, washed with brine, dried over MgSO_4 , filtered and concentrated. The residue was dissolved in CH_2Cl_2 and to it was added hexanes. The resulting precipitate was collected by vacuum filtration and then high vacuum dried to afford 220 mg of the title compound. MS (m/z) 635.36 $[\text{M}+\text{H}]^+$.

Synthesis of (S)-5-(2-(1-(2-(4-acetyl-3-(trifluoromethyl)-1H-pyrazol-1-yl)acetamido)-2-(3,5-difluorophenyl)ethyl)pyridin-3-yl)-2-fluorobenzamide (**389B**):

Compound 389 A (120 mg, 0.19 mmol) was dissolved in 5 mL of THF and to it was added MeMgBr (3.0 M in diethyl ether, 0.67 mL, 2 mmol) and the reaction mixture was stirred at ambient temperature for 20 min. It was quenched with ice and 1 N HCl and extracted with EtOAc. 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 25 mg of the title compound. MS (m/z) 590.09 $[\text{M}+\text{H}]^+$. ^1H NMR (400 MHz, CDCl_3) δ 10.00 (d, $J = 7.3$ Hz, 1H), 8.91 – 8.67 (m, 1H), 8.10 – 7.96 (m, 2H), 7.80 (m,

2H), 7.61 (d, $J = 6.1$ Hz, 1H), 7.31 (dd, $J = 11.2, 8.6$ Hz, 1H), 6.90 (m, 1H), 6.61 (m, 2H), 6.21 (d, $J = 5.7$ Hz, 2H), 5.47 (dd, $J = 16.0, 7.4$ Hz, 1H), 4.91 (q, $J = 16.2$ Hz, 2H), 3.20 (dd, $J = 13.6, 7.1$ Hz, 1H), 3.03 (dd, $J = 13.5, 9.0$ Hz, 1H), 2.45 (s, 3H).

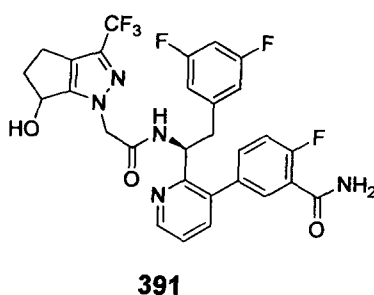
5 Example 390



Synthesis of 5-(2-(1-(2-(3-(difluoromethyl)-4,7,7-trifluoro-4,5,6,7-tetrahydro-1H-indazol-1-yl)acetamido)-2-(3,5-difluorophenyl)ethyl)pyridin-3-yl)-2-fluorobenzamide (**390**):

- 10 Compound 390 was prepared according to the method presented in the synthesis of Example 150 utilizing Compound 334 to provide 17 mg of the title compound. MS (m/z) 638.19 $[M+H]^+$. 1H NMR (400 MHz, cd_3od) δ 8.71 (d, $J = 4.9$ Hz, 1H), 7.65 (d, $J = 7.8$ Hz, 1H), 7.51 – 7.41 (m, 1H), 7.39 – 7.26 (m, 2H), 7.21 (dd, $J = 10.7, 8.6$ Hz, 1H), 6.98 – 6.55 (m, 2H), 6.31 (d, $J = 6.7$ Hz, 2H), 5.72 (d, 1H), 5.35 (t, $J = 6.7$ Hz, 1H), 5.13 – 4.97 (m, 2H), 3.07 (m, 2H), 2.68 – 2.05 (m, 4H).

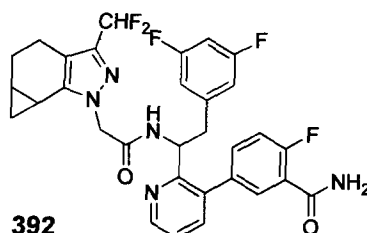
Example 391



- 20 Synthesis of 5-(2-((1S)-2-(3,5-difluorophenyl)-1-(2-(6-hydroxy-3-(trifluoromethyl)-5,6-dihydrocyclopenta[c]pyrazol-1(4H)-yl)acetamido)ethyl)pyridin-3-yl)-2-fluorobenzamide (**391**): Compound 391 was prepared according to the method presented for the synthesis of Example 325 utilizing Compound 281C to afford 15 mg of the title compound: MS (m/z) 604.36 $[M+H]^+$. 1H NMR (400 MHz, cd_3od) δ 8.71 (dt, $J = 4.9, 1.6$ Hz, 1H), 7.70 (td, $J = 8.5, 1.6$ Hz, 1H), 7.48 (m, 2H), 7.33 (bs, 1H), 7.22 (m, 1H), 6.66 (td, $J = 9.3, 7.0$ Hz, 1H), 6.30 (dd, $J = 8.3,$

6.3 Hz, 2H), 5.36 (dd, $J = 15.6, 8.1$ Hz, 1H), 5.07 (dt, $J = 7.2, 3.5$ Hz, 1H), 4.95 – 4.76 (m, 2H), 3.15 – 2.98 (m, 2H), 2.97 – 2.70 (m, 2H), 2.68 – 2.46 (m, 1H), 2.36 (m, 1H).

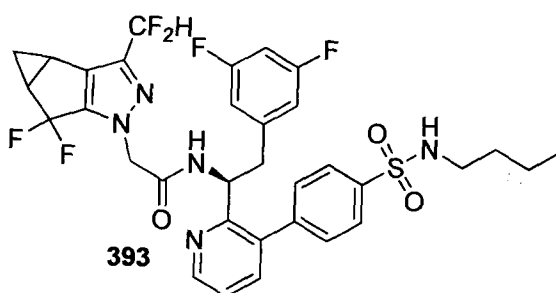
Example 392



Synthesis of 5-(2-(1-(2-(3-(difluoromethyl)-5,5a,6,6a-tetrahydrocyclopropa[g]indazol-1(4H)-yl)acetamido)-2-(3,5-difluorophenyl)ethyl)pyridin-3-yl)-2-fluorobenzamide (**392**):

Compound **392** was prepared according to the method presented in the synthesis of Example 54 utilizing Compound **54B** and 2-(3-(difluoromethyl)-5,5a,6,6a-tetrahydrocyclopropa[g]indazol-1(4H)-yl)acetic acid (Compound **299C**) to provide 22 mg of the title compound. MS (m/z) 596.43 $[M+H]^+$. 1H NMR (400 MHz, cd_3od) δ 8.82 – 8.57 (m, 1H), 7.68 (dd, $J = 8.9, 3.8$ Hz, 1H), 7.54 – 7.41 (m, 2H), 7.34 (bs, 1H), 7.30 – 7.13 (m, 1H), 6.83 – 6.42 (m, 2H), 6.33 (m, 2H), 5.37 (dd, $J = 13.4, 7.6$ Hz, 1H), 4.97 – 4.73 (m, 2H), 3.14 – 2.98 (m, 2H), 2.70 (d, $J = 14.7$ Hz, 1H), 2.24 – 1.93 (m, 2H), 1.94 – 1.48 (m, 3H), 0.93 (m, 1H), 0.64 (m, 1H).

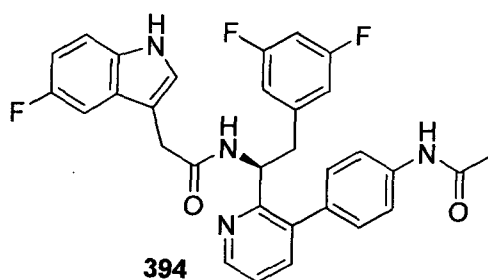
Example 393



Synthesis of (S)-N-(1-(3-(4-(N-butylsulfamoyl)phenyl)-pyridin-2-yl)-2-(3,5-difluorophenyl)ethyl)-2-(3-(difluoromethyl)-5,6-dihydro-4,5-(methano)-6,6-difluorocyclopenta[c]pyrazol-1(4H)-yl)acetamide (**393**):

Prepared 2.5 mg of the title compound by a method analogous to **68B** using **68A** and 4-(N-butylsulfamoyl)phenylboronic acid. MS (m/z) 692 $[M+H]^+$.

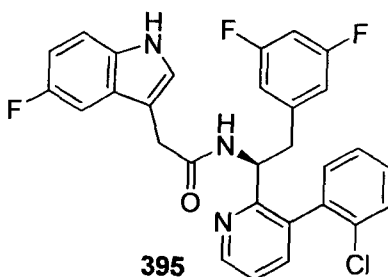
Example 394



Synthesis of ((S)-N-(1-(3-(4-acetamidophenyl)pyridin-2-yl)-2-(3,5-difluorophenyl)ethyl)-2-(5-fluoro-1H-indol-3-yl)acetamide (**394**):

Prepared 37.1 mg of the title compound by a method analogous to **55F** using 4-(acetamidophenyl)boronic acid and **55E**. MS (m/z) 543 $[M+H]^+$.

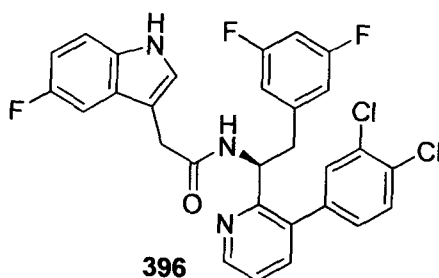
Example 395



Synthesis of (S)-N-(1-(3-(2-chlorophenyl)pyridin-2-yl)-2-(3,5-difluorophenyl)ethyl)-2-(5-fluoro-1H-indol-3-yl)acetamide (**395**):

Prepared 37.1 mg of the title compound by a method analogous to **55F** using 2-chlorophenylboronic acid and **55E**. MS (m/z) 520 $[M+H]^+$.

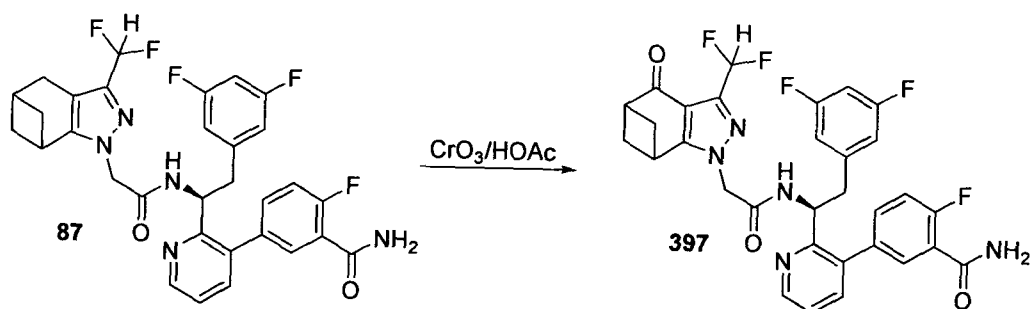
Example 396



Synthesis of (S)-N-(1-(3-(3,4-dichlorophenyl)pyridin-2-yl)-2-(3,5-difluorophenyl)ethyl)-2-(5-fluoro-1H-indol-3-yl)acetamide (**396**):

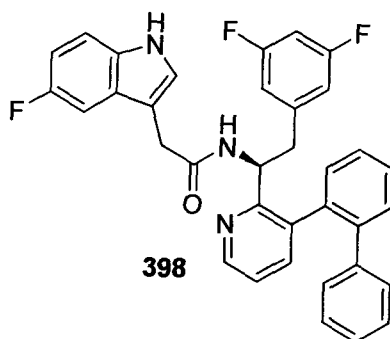
Prepared 15.4 mg of the title compound by a method analogous to **55F** using 3,4-dichlorophenylboronic acid and **55E**. MS (m/z) 554 $[M+H]^+$.

Example 397



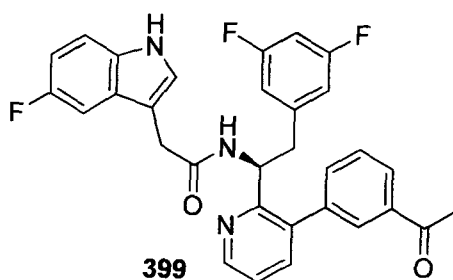
- 5 Synthesis of (S)-5-(2-(2-(3,5-difluorophenyl)-1-(2-(4,5,6,7-tetrahydro-3-difluoromethyl-4-oxo-5,7-(methano)indazol-1-yl)acetamido)ethyl)pyridin-3-yl)-2-fluorobenzamide (**397**):
To a solution of Compound 87 (20.7 mg, 0.029 mmol) in acetic acid (1 ml) was added CrO₃ (8.7 mg, 0.087 mmol). The reaction mixture was stirred at room temperature for 7 days and then filtered. The filtrate was purified by RP HPLC using a C18 column with a gradient of 0.1%
10 TFA-acetonitrile/0.1%/H₂O to give 10.3 mg of the title compound. MS (*m/z*) 610 [M+H]⁺.

Example 398



- Synthesis of (S)-N-(1-(3-(biphenyl-2-yl)pyridin-2-yl)-2-(3,5-difluorophenyl)ethyl)-2-(5-fluoro-1H-indol-3-yl)acetamide (**398**):
15 Prepared 36.3 mg of the title compound by a method analogous to **55F** using 2-phenylphenylboronic acid and **55E**. MS (*m/z*) 562 [M+H]⁺.

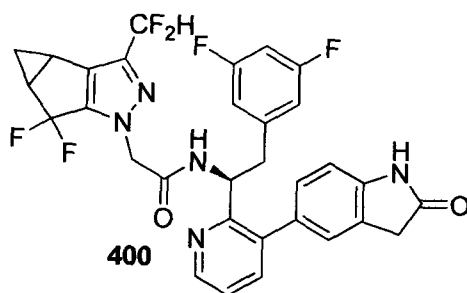
Example 399



Synthesis of ((S)-N-(2-(3,5-difluorophenyl)-1-(6'-fluoro-5'-methyl-3,3'-bipyridin-2-yl)ethyl)-2-(5-fluoro-1H-indol-3-yl)acetamide (**399**):

- 5 Prepared 31.9 mg of the title compound by analogous method to **55F** using 3-acetylphenylboronic acid and **55E**. MS (m/z) 519 $[M+H]^+$.

Example 400

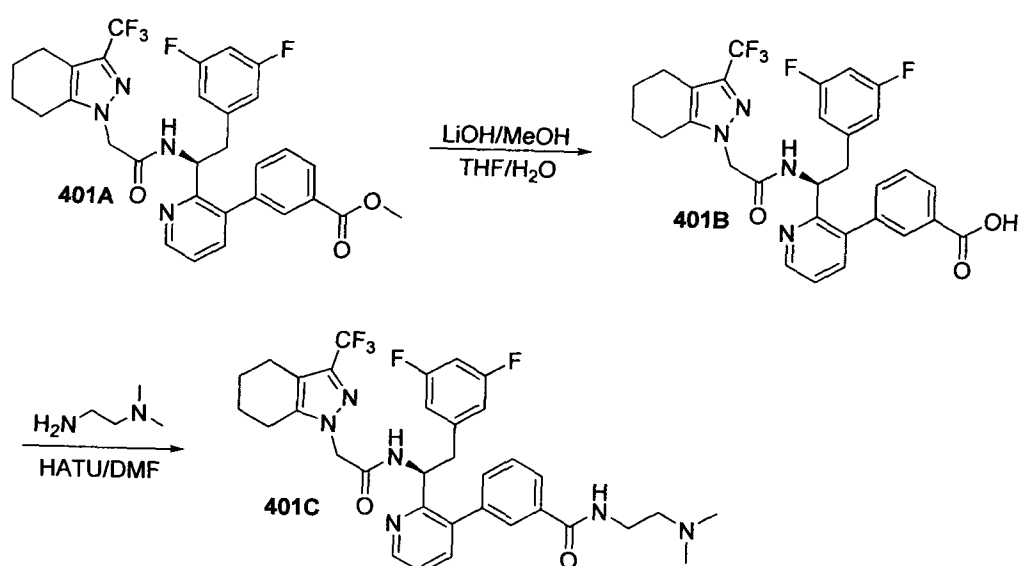


- 10 Synthesis of (S)-N-(1-(3-(oxindole-5-yl)-pyridin-2-yl)-2-(3,5-difluorophenyl)ethyl)-2-(3-(difluoromethyl)-5,6-dihydro-4,5-(methano)-6,6-difluoro-cyclopenta[c]pyrazol-1(4H)-yl)acetamide (**400**):

Prepared 4.8 mg of the title compound by a method analogous to **68B** using **68A** and oxindole-5-boronic acid, pinacol ester. MS (m/z) 612 $[M+H]^+$.

15

Example 401



Synthesis of (S)-methyl 3-(2-(2-(3,5-difluorophenyl)-1-(2-(3-(trifluoromethyl)-4,5,6,7-tetrahydro-1H-indazol-1-yl)acetamido)ethyl)pyridin-3-yl)benzoate (**401A**):

Prepared 480 mg of the title compound by a method analogous to **57B** using 3-carbomethoxyphenylboronic acid and **57A**. MS (*m/z*) 599 [M+H]⁺.

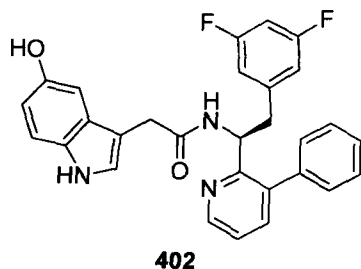
Synthesis of (S)-3-(2-(2-(3,5-difluorophenyl)-1-(2-(3-(trifluoromethyl)-4,5,6,7-tetrahydro-1H-indazol-1-yl)acetamido)ethyl)pyridin-3-yl)benzoic acid (**401B**):

Dissolved **410A** (480 mg, 0.803 mmol) in THF (4 ml) and MeOH (2 ml). Added 2.5N aq. LiOH and stirred for 45 min. at room temperature. The reaction was acidified to pH=6 with 20 mM KH₂PO₄. The mixture was extracted 3x EtOAc. The combined organics were washed with brine, dried over MgSO₄, filtered and concentrated. The residue was dried under reduced pressure to give 348 mg of the title compound. MS (*m/z*) 585 [M+H]⁺.

Synthesis of (S)-3-(2-(2-(3,5-difluorophenyl)-1-(2-(3-(trifluoromethyl)-4,5,6,7-tetrahydro-1H-indazol-1-yl)acetamido)ethyl)pyridin-3-yl)-N-(2-(dimethylamino)ethyl)benzamide (**401C**):

Dissolved **401B** (30 mg, 0.051 mmol) in 1ml of DMF. Added N,N-dimethylaminoethylamine (16.8 μ L, 0.153 mmol) followed by HATU (21 mg, 0.056 mmol). Stirred the reaction for 1 hr at room temperature. Filtered reaction and purified filtrate by RP HPLC using a C18 column with a gradient of 0.1%/H₂O, 0.1% TFA-acetonitrile to give 24.1 mg of the title compound. ¹H NMR (400 MHz, CD₃OD) δ 8.71 (d, 1H), 7.89 (d, 1H), 7.72 (s, 1H), 7.62 (d, 1H), 7.52 (t, 1H), 7.40 (dd, 1H), 7.23 (d, 1H), 6.68 (t, 1H), 6.26 (d, 2H), 5.52 (t, 1H), 3.66 (d, 2H), 3.01 (dd, 2H), 2.89 (d, 5H), 2.55 (s, 2H), 2.42 (d, 2H), 1.76 (s, 4H). MS (*m/z*) 655 [M+H]⁺.

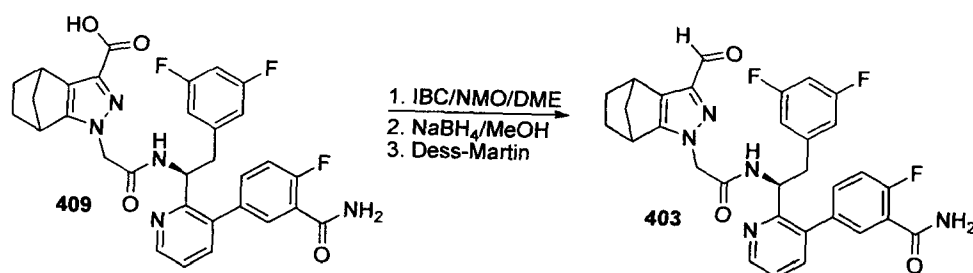
Example 402



Synthesis of (S)-N-(2-(3,5-difluorophenyl)-1-(3-phenylpyridin-2-yl)ethyl)-2-(5-hydroxy-1H-indol-3-yl)acetamide (**402**):

- 5 Prepared 44 mg of the title compound by a method analogous to **113** using phenylboronic acid. ¹H NMR (*d*-DMSO, 400 MHz) δ 10.47 (1H, s), 8.615 (1H, dd), 8.40 (1H, d), 7.53 (1H, dd), 7.35 (3H, m), 7.15 (2H, m), 7.05 (1H, d), 6.91 (2H, mm), 6.76 (1H, d), 6.53 (1H, dd), 6.31 (2H, d), 5.22 (2H, q), 4.34 (1H, b), 3.39 (1H, s), 2.87 (2H, d). MS (*m/z*) 484 [M+H]⁺.

10 Example 403

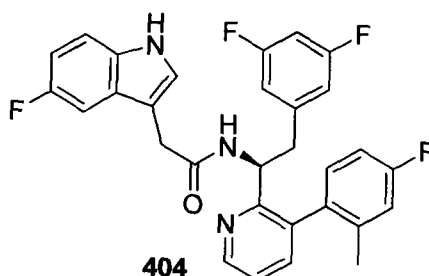


Synthesis of (S)-5-(2-(2-(3,5-difluorophenyl)-1-(2-(4,5,6,7-tetrahydro-3-formyl-4,7-(methano)indazol-1-yl)acetamido)ethyl)pyridin-3-yl)-2-fluorobenzamide (**403**):

- 15 To a 0 °C solution of Compound 409 (200 mg, 0.34 mmol) in DME (680 μ l) was added N-methylmorpholine (37 μ l, 0.34 mmol) and isobutylchloroformate (45 μ l, 0.34 mmol). The reaction was stirred at 0 °C for 5 min. then filtered to remove the precipitate. Washed the precipitate 3x DME (2 ml total). To the combined filtrates was added NaBH₄ (19.3 mg, 0.51 mmol) in H₂O. The reaction was stirred 5 min. at room temperature. An additional 5.8 mg of NaBH₄ was added to drive the reaction to completion. The reaction mixture was partitioned
- 20 between EtOAc and H₂O. Extracted the aqueous layer 2x EtOAc. The combined organics were washed with brine, dried over MgSO₄, filtered and concentrated. The residue on purified on SiO₂ using MeOH/CH₂Cl₂ to give 108 mg of (S)-5-(2-(2-(3,5-difluorophenyl)-1-(2-(4,5,6,7-tetrahydro-3-hydroxymethyl-4,7-(methano)indazol-1-yl)acetamido)ethyl)pyridin-3-yl)-2-fluorobenzamide. This material was dissolved in CH₂Cl₂ and treated with Dess-Martin

periodinane (85.8 mg, 0.20 mmol) at room temperature for 1 hr. The reaction mixture was filtered and concentrated. The residue was re-dissolved in EtOAc and extracted 2x H₂O and 1x brine, dried over MgSO₄, filtered and concentrated. Purified 7 mg of crude by RP HPLC using a C18 column with a gradient of 0.1%/H₂O, 0.1% TFA-acetonitrile to give 3.2 mg of the title compound. MS (*m/z*) 574 [M+H]⁺. The 100 mg remaining was used crude.

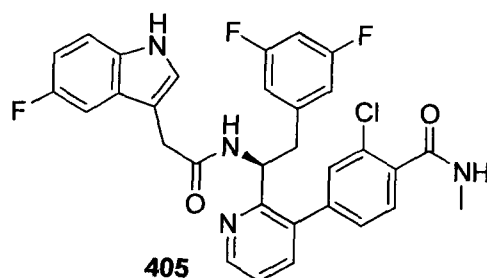
Example 404



Synthesis of (S)-N-(2-(3,5-difluorophenyl)-1-(3-(4-fluoro-2-methylphenyl)pyridin-2-yl)ethyl)-2-(5-fluoro-1H-indol-3-yl)acetamide (**404**):

Prepared 2 mg the title compound by a method analogous to **55F** using (4-fluoro-2-methylphenyl)-boronic acid (15.3 mg, 0.10 mmol) and **55E** (40.7 mg, 0.83 mmol). MS (*m/z*) 518 [M+H]⁺.

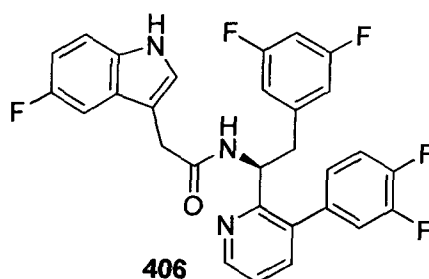
Example 405



Synthesis of (S)-2-chloro-4-(2-(2-(3,5-difluorophenyl)-1-(2-(5-fluoro-1H-indol-3-yl)acetamido)ethyl)pyridin-3-yl)-N-methylbenzamide (**405**):

Prepared 8 mg of the title compound by a method analogous to **55F** using 3-chloro-4-(methylcarbamoyl)phenylboronic acid and **55E**. MS (*m/z*) 578 [M+H]⁺.

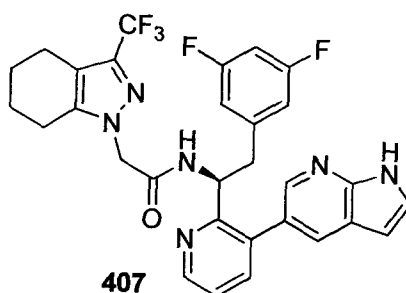
Example 406



Synthesis of (S)-N-(2-(3,5-difluorophenyl)-1-(3-(3,4-difluorophenyl)pyridin-2-yl)ethyl)-2-(5-fluoro-1H-indol-3-yl)acetamide (**406**):

Prepared 28.1 mg of the title compound by a method analogous to **55F** using 3,4-difluorophenylboronic acid and **55E**. MS (m/z) 522 $[M+H]^+$.

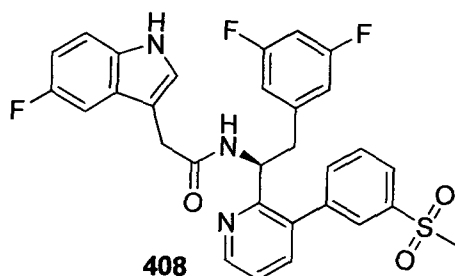
Example 407



Synthesis of (S)-N-(1-(3-(1H-pyrrolo[2,3-b]pyridin-5-yl)pyridin-2-yl)-2-(3,5-difluorophenyl)ethyl)-2-(3-(trifluoromethyl)-4,5,6,7-tetrahydro-1H-indazol-1-yl)acetamide (**407**):

Prepared 1.4 mg of the title compound by a method analogous to **57B** using **57A** and 1H-pyrrolo[2,3-b]pyridin-5-ylboronic acid. MS (m/z) 583 $[M+H]^+$.

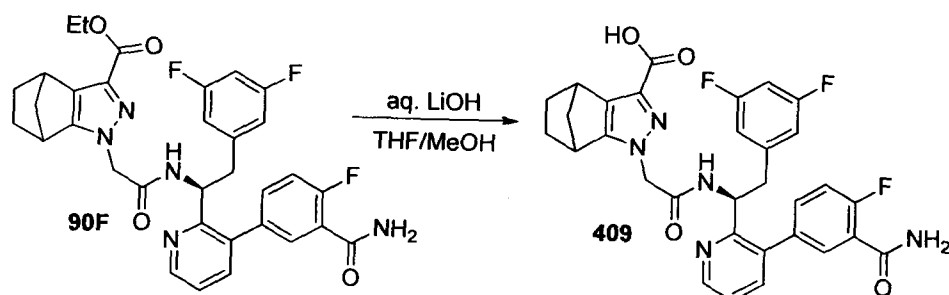
Example 408



Synthesis of (S)-N-(2-(3,5-difluorophenyl)-1-(3-(4-(methylsulfonyl)phenyl)pyridin-2-yl)ethyl)-2-(5-fluoro-1H-indol-3-yl)acetamide (**408**):

Prepared 24 mg of the title compound by analogous method to **55F** using 3-(methylsulfonyl)boronic acid and **55E**. MS (m/z) 564 $[M+H]^+$.

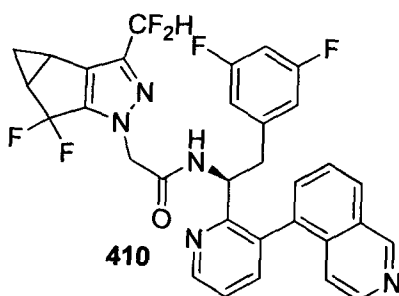
Example 409



Synthesis of (S)-5-(2-(2-(3,5-difluorophenyl)-1-(2-(4,5,6,7-tetrahydro-3-carboxy-4,7-(methano)indazol-1-yl)acetamido)ethyl)pyridin-3-yl)-2-fluorobenzamide (**409**):

Prepared 209 mg of the title compound by a method analogous to **74C** using compound **90F**. MS (m/z) 590 $[M+H]^+$.

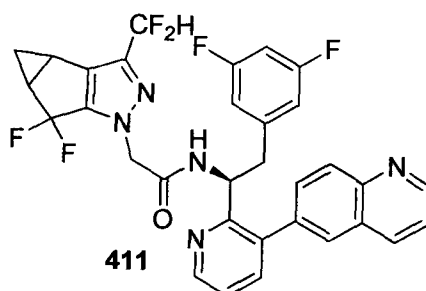
Example 410



Synthesis of (S)-N-(1-(3-(quinole-5-yl)-pyridin-2-yl)-2-(3,5-difluorophenyl)ethyl)-2-(3-(difluoromethyl)-5,6-dihydro-4,5-(methano)-6,6-difluoro-cyclopenta[c]pyrazol-1(4H)-yl)acetamide (**410**):

Prepared 19.8 mg of the title compound by a method analogous to **68B** using **68A** and quinoline-5-boronic acid. MS (m/z) 608 $[M+H]^+$.

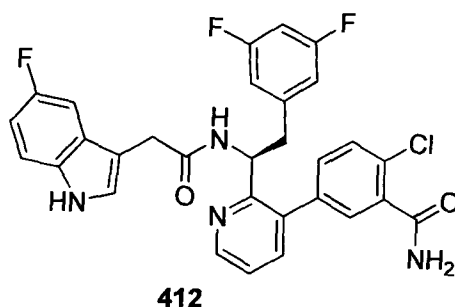
Example 411



Synthesis of (S)-N-(1-(3-(quinoline-6-yl)-pyridin-2-yl)-2-(3,5-difluorophenyl)ethyl)-2-(3-(difluoromethyl)-5,6-dihydro-4,5-(methano)-6,6-difluoro-cyclopenta[c]pyrazol-1(4H)-yl)acetamide (**411**):

- 5 Prepared 6.1 mg of the title compound by a method analogous to **68B** using **68A** and quinoline-6-boronic acid. MS (m/z) 608 $[M+H]^+$.

Example 412

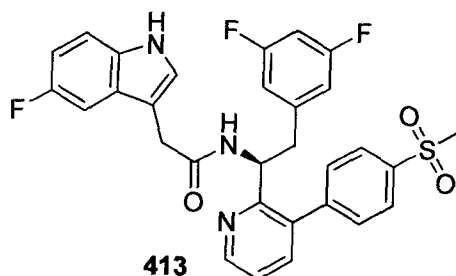


- 10 Synthesis of (S)-2-chloro-5-(2-(2-(3,5-difluorophenyl)-1-(2-(5-fluoro-1H-indol-3-yl)acetamido)ethyl)pyridin-3-yl)benzamide (**412**):

Prepared 37 mg of the title compound by a method analogous to **55F** using 4-chloro-3-carbamoylphenyl boronic acid. ^1H NMR (400 MHz, d_6 -DMSO) δ 10.87 (s, 1H), 8.79 – 8.55 (m, 2H), 7.81 (s, 1H), 7.56 (dd, 2H), 7.46 – 7.31 (m, 3H), 7.28 – 7.00 (m, 4H), 6.96 – 6.74 (m, 3H), 6.51 (d, 2H), 5.14 (q, 1H), 3.42 (s, 2H), 2.98 (d, 2H). MS (m/z) 563 $[M+H]^+$.

- 15

Example 413

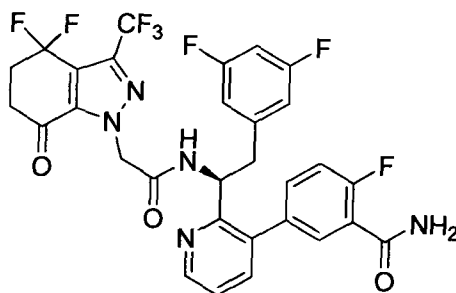


Synthesis of (S)-N-(2-(3,5-difluorophenyl)-1-(3-(4-(methylsulfonyl)phenyl)pyridin-2-yl)ethyl)-2-(5-fluoro-1H-indol-3-yl)acetamide (**413**):

Prepared 16.1 mg of the title compound by a method analogous to **55F** using 4-(methylsulfonyl)boronic acid and **55E**. MS (m/z) 564 $[M+H]^+$.

5

Example 414

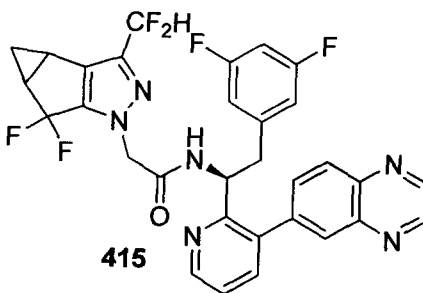


Synthesis of (S)-5-(2-(1-(2-(3-(difluoromethyl)-4,4-difluoro-7-oxo-4,5,6,7-tetrahydro-1H-indazol-1-yl)acetamido)-2-(3,5-difluorophenyl)ethyl)pyridin-3-yl)-2-fluorobenzamide (**414**):

Prepared 6 mg of the title compound by a method analogous to **397** using compound **102D**. MS (m/z) 652.4 $[M+H]^+$.

10

Example 415

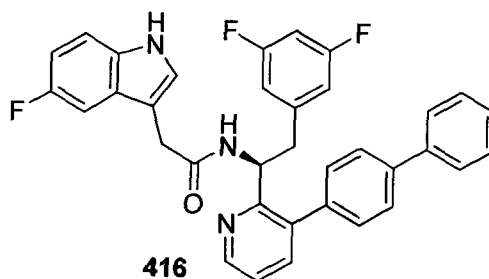


Synthesis of (S)-N-(1-(3-(quinoxalin-6-yl)-pyridin-2-yl)-2-(3,5-difluorophenyl)ethyl)-2-(3-(difluoromethyl)-5,6-dihydro-4,5-(methano)-6,6-difluoro-cyclopenta[c]pyrazol-1(4H)-yl)acetamide (**415**):

Prepared 5.1 mg of the title compound by a method analogous to **68B** using **68A** and 6-(4,4,5,5-Tetramethyl-1,3,2-dioxaborolan-2-yl)quinoxaline. MS (m/z) 609 $[M+H]^+$.

20

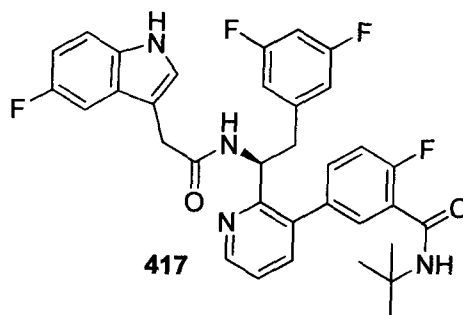
Example 416



Synthesis of (S)-N-(1-(3-(biphenyl-4-yl)pyridin-2-yl)-2-(3,5-difluorophenyl)ethyl)-2-(5-fluoro-1H-indol-3-yl)acetamide (**416**):

Prepared 27 mg of the title compound by a method analogous to **55F** using 4-phenyl-
 5 phenylboronic acid and **55E**. MS (m/z) 562 $[M+H]^+$.

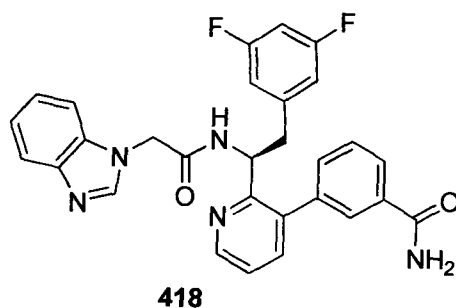
Example 417



Synthesis of (S)-N-tert-butyl-5-(2-(2-(3,5-difluorophenyl)-1-(2-(5-fluoro-1H-indol-3-yl)acetamido)ethyl)pyridin-3-yl)-2-fluorobenzamide (**417**):

Prepared 34.9 mg of the title compound by a method analogous to **55F** using 3-(tert-butylcarbamoyl)-4-fluorophenylboronic acid and **55E**. MS (m/z) 603 $[M+H]^+$.

Example 418

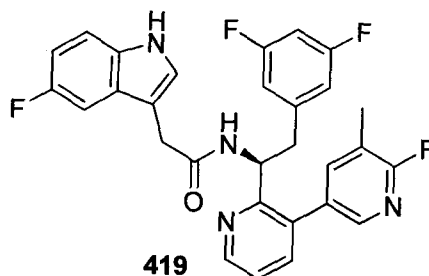


Synthesis of (S)-3-(2-(1-(2-(1H-benzo[d]imidazol-1-yl)acetamido)-2-(3,5-difluorophenyl)ethyl)pyridin-3-yl)benzamide (**418**):

Prepared 30 mg of the title compound by a method analogous to **50D** using benzimidazole-1-acetic acid and **50C**. ^1H NMR (400 MHz, dmso) δ 9.28 (d, 1H), 9.19 (s, 1H), 8.73 (dd, 1H), 8.03

– 7.81 (m, 2H), 7.80 – 7.59 (m, 3H), 7.53 – 7.29 (m, 6H), 6.94 (t, 1H), 6.57 (d, 2H), 5.24 – 5.07 (m, 3H), 3.05 (ddd, 2H). MS (m/z) 512 [$M+H$]⁺.

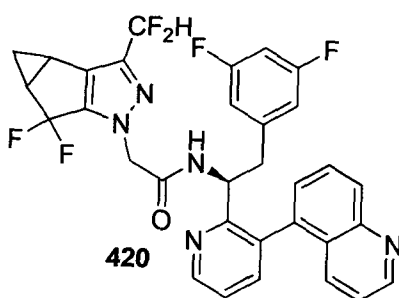
Example 419



Synthesis of ((S)-N-(2-(3,5-difluorophenyl)-1-(6'-fluoro-5'-methyl-3,3'-bipyridin-2-yl)ethyl)-2-(5-fluoro-1H-indol-3-yl)acetamide (**419**):

Prepared 26.7 mg of the title compound by a method analogous to **55F** using 2-Fluoro-3-methylpyridine-5-boronic acid and **55E**. MS (m/z) 519 [$M+H$]⁺.

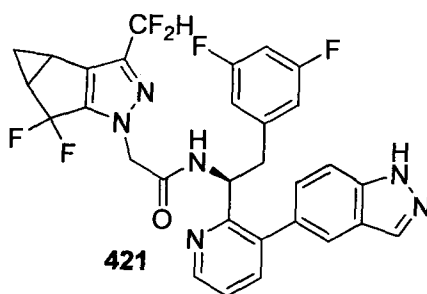
Example 420



Synthesis of (S)-N-(1-(3-(isoquinoline-5-yl)-pyridin-2-yl)-2-(3,5-difluorophenyl)ethyl)-2-(3-(difluoromethyl)-5,6-dihydro-4,5-(methano)-6,6-difluoro-cyclopenta[c]pyrazol-1(4H)-yl)acetamide (**420**):

Prepared 17.4 mg of the title compound by a method analogous to **68B** using **68A** and isoquinoline-5-boronic acid. MS (m/z) 608 [$M+H$]⁺.

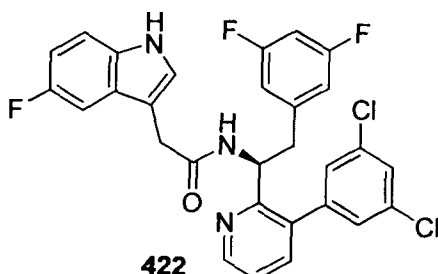
Example 421



Synthesis of (S)-N-(1-(3-(indazol-5-yl)-pyridin-2-yl)-2-(3,5-difluorophenyl)ethyl)-2-(3-(difluoromethyl)-5,6-dihydro-4,5-(methano)-6,6-difluoro-cyclopenta[c]pyrazol-1(4H)-yl)acetamide (**421**):

Prepared 3 mg of the title compound by a method analogous to **68B** using **68A** and indazole-5-boronic acid. MS (m/z) 597 [$M+H$]⁺.

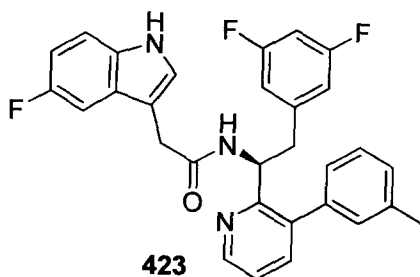
Example 422



Synthesis of ((S)-N-(1-(3-(3,5-dichlorophenyl)pyridin-2-yl)-2-(3,5-difluorophenyl)ethyl)-2-(5-fluoro-1H-indol-3-yl)acetamide (**422**):

Prepared 25.2 mg of the title compound by a method analogous to **55F** using 3,5-dichlorophenylboronic acid and **55E**. MS (m/z) 554 [$M+H$]⁺.

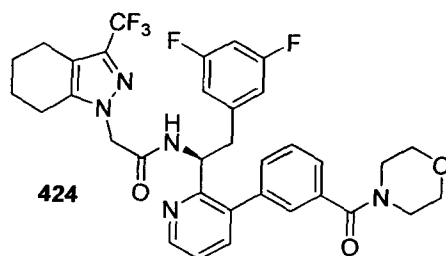
Example 423



Synthesis of (S)-N-(2-(3,5-difluorophenyl)-1-(3-p-tolylpyridin-2-yl)ethyl)-2-(5-fluoro-1H-indol-3-yl)acetamide (**423**):

Prepared 34 mg of the title compound by a method analogous to **55F** using 4-methylphenylboronic acid and **55E**. MS (m/z) 500 $[M+H]^+$.

Example 424



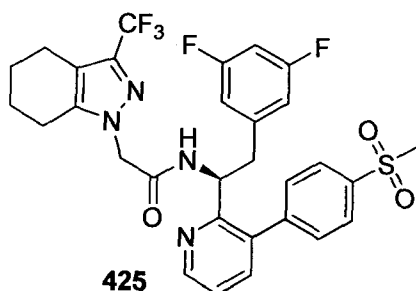
5

Synthesis of (S)-N-(2-(3,5-difluorophenyl)-1-(3-(3-(morpholine-4-carbonyl)phenyl)pyridin-2-yl)ethyl)-2-(3-(trifluoromethyl)-4,5,6,7-tetrahydro-1H-indazol-1-yl)acetamide (**424**):

Prepared 20.9 mg of the title compound by a method analogous to **401C** using **401B** and morpholine. ^1H NMR (400 MHz, CD_3OD) δ 8.71 (d, 1H), 7.89 (d, 1H), 7.72 (s, 1H), 7.62 (d, 1H), 7.52 (t, 1H), 7.40 (dd, 1H), 7.23 (d, 1H), 6.68 (t, 1H), 6.26 (d, 2H), 5.52 (t, 1H), 3.66 (d, 2H), 3.01 (dd, 2H), 2.89 (d, 5H), 2.55 (s, 2H), 2.42 (d, 2H), 1.76 (s, 4H). MS (m/z) 654 $[M+H]^+$.

10

Example 435

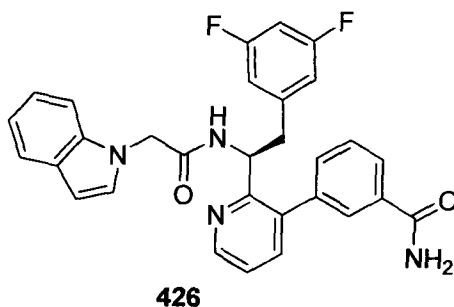


425

15 Synthesis of (S)-N-(2-(3,5-difluorophenyl)-1-(3-(4-(methylsulfonyl)phenyl)pyridin-2-yl)ethyl)-2-(3-(trifluoromethyl)-4,5,6,7-tetrahydro-1H-indazol-1-yl)acetamide (**425**):

Prepared 11.9 mg of the title compound by a method analogous to compound **57B** using **57A** and 4-methylsulfonylphenyl boronic acid. MS (m/z) 619 $[M+H]^+$.

20 Example 426

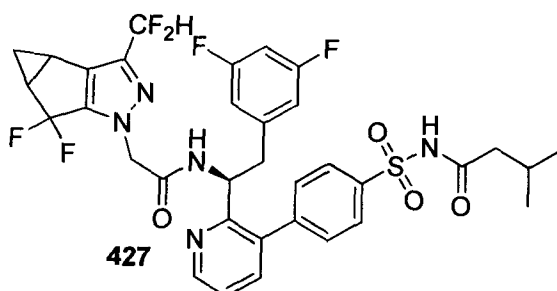


Synthesis of (S)-3-(2-(1-(2-(1H-indol-1-yl)acetamido)-2-(3,5-difluorophenyl)ethyl)pyridin-3-yl)benzamide (426):

Prepared 35 mg of the title compound by a method analogous to **50D** using indole-1-acetic acid.

- 5 ^1H NMR (400 MHz, dmso) δ 10.82 (s, 1H), 8.66 (dd, 2H), 7.92 (d, 1H), 7.86 (s, 1H), 7.75 (s, 1H), 7.61 (dd, 1H), 7.49 – 7.35 (m, 4H), 7.26 (dd, 1H), 7.05 – 6.98 (m, 2H), 6.91 (t, 1H), 6.74 – 6.61 (m, 1H), 6.49 (d, 2H), 5.17 (dd, 3H), 4.70 – 4.65 (m, 1H), 3.44 (q, 2H), 2.95 (d, 2H). MS (m/z) 529 $[\text{M}+\text{H}]^+$.

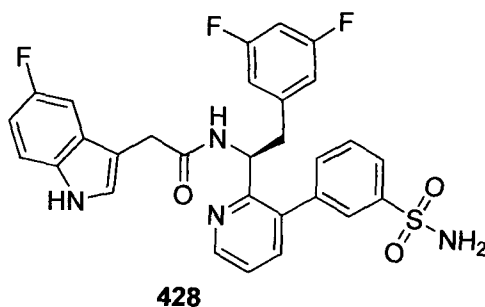
10 Example 427



Synthesis of (S)-N-(1-(3-(4-(N-(3-methylbutanoyl)sulfamoyl)phenyl)-pyridin-2-yl)-2-(3,5-difluorophenyl)ethyl)-2-(3-(difluoromethyl)-5,6-dihydro-4,5-(methano)-6,6-difluorocyclopenta[c]pyrazol-1(4H)-yl)acetamide (427):

- 15 Prepared 11.6 mg of the title compound by a method analogous to **68B** using **68A** and 4-(N-(3-methylbutanoyl)sulfamoyl)phenylboronic acid. MS (m/z) 720 $[\text{M}+\text{H}]^+$.

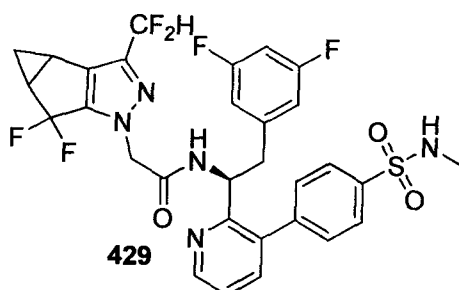
Example 428



Synthesis of (S)-N-(2-(3,5-difluorophenyl)-1-(3-(3-sulfamoylphenyl)pyridin-2-yl)ethyl)-2-(5-fluoro-1H-indol-3-yl)acetamide (**428**):

Prepared 43 mg of the title compound by analogous method to **55F** using 3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzenesulfonamide. ¹H NMR (400 MHz, D6-DMSO) δ 10.87 (s, 9H), 8.69 (dd, J = 9.5, 4.9 Hz, 19H), 7.82 (d, J = 7.7 Hz, 10H), 7.68 (s, 11H), 7.61 – 7.16 (m, 69H), 7.13 – 7.02 (m, 19H), 6.93 – 6.78 (m, 22H), 6.52 (d, J = 6.4 Hz, 31H), 5.13 (dd, J = 14.9, 7.9 Hz, 13H), 3.50 – 3.33 (m, 20H), 3.10 – 2.86 (m, 21H), 2.05 (s, 6H), 1.26 – 0.77 (m, 19H). MS (m/z) 565 [M+H]⁺.

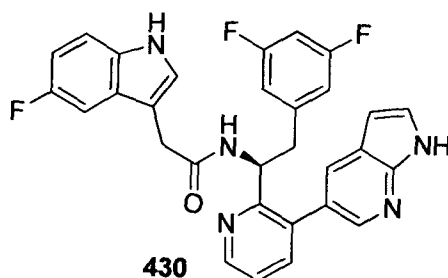
10 Example 429



Synthesis of (S)-N-(1-(3-(4-(N-methylsulfamoyl)phenyl)-pyridin-2-yl)-2-(3,5-difluorophenyl)ethyl)-2-(3-(difluoromethyl)-5,6-dihydro-4,5-(methano)-6,6-difluorocyclopenta[c]pyrazol-1(4H)-yl)acetamide (**429**):

Prepared 17.3 mg of the title compound by a method analogous to **68B** using **68A** and 4-(N-methylsulfamoyl)phenylboronic acid pinacol ester. MS (m/z) 650 [M+H]⁺.

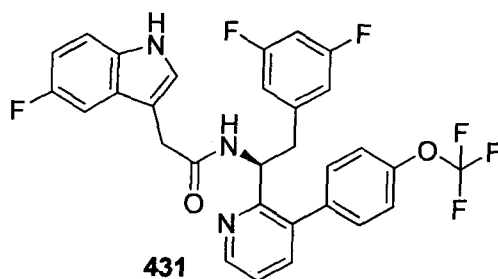
Example 430



Synthesis of (S)-N-(1-(3-(1H-pyrrolo[2,3-b]pyridin-5-yl)pyridin-2-yl)-2-(3,5-difluorophenyl)ethyl)-2-(5-fluoro-1H-indol-3-yl)acetamide (**430**):

Prepared 26.7 mg of the title compound by analogous method to **55F** using 5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrrolo[2,3-b]pyridine and **55E**. MS (m/z) 526 [M+H]⁺.

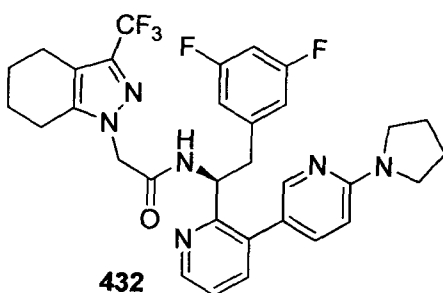
Example 431



5 Synthesis of (S)-N-(2-(3,5-difluorophenyl)-1-(3-(4-(trifluoromethoxy)phenyl)pyridin-2-yl)ethyl)-2-(5-fluoro-1H-indol-3-yl)acetamide (**431**):

Prepared 38 mg of the title compound by a method analogous to **55F** using 3-trifluoromethoxyphenyl boronic acid and **55E**. MS (m/z) 570 $[M+H]^+$.

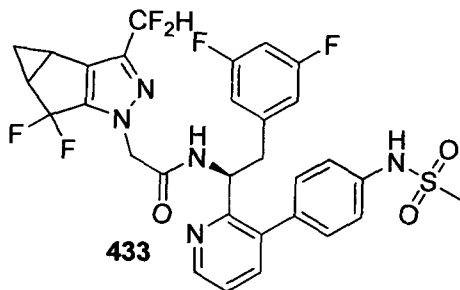
Example 432



10 Synthesis of (S)-N-(2-(3,5-difluorophenyl)-1-(6'-(pyrrolidin-1-yl)-3,3'-bipyridin-2-yl)ethyl)-2-(3-(trifluoromethyl)-4,5,6,7-tetrahydro-1H-indazol-1-yl)acetamide (**432**):

Prepared 16.3 mg of the title compound by a method analogous to compound **57B** using **57A** and 6-(pyrrolidin-1-yl)pyridin-3-ylboronic acid. MS (m/z) 611 $[M+H]^+$.

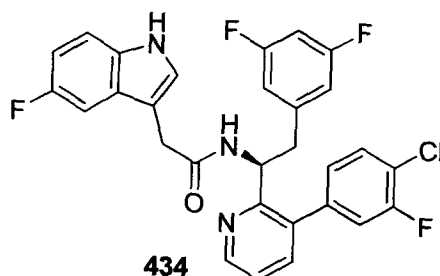
Example 433



20 Synthesis of (S)-N-(1-(3-(4-(methylsulfonamido)phenyl)-pyridin-2-yl)-2-(3,5-difluorophenyl)ethyl)-2-(3-(difluoromethyl)-5,6-dihydro-4,5-(methano)-6,6-difluorocyclopenta[c]pyrazol-1(4H)-yl)acetamide (**433**):

Prepared 20.6 mg of the title compound by a method analogous to **68B** using **68A** and N-4-methanesulfonamidophenylboronic acid. MS (*m/z*) 650 [M+H]⁺.

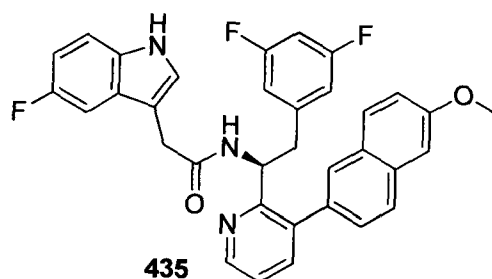
Example 434



Synthesis of (S)-N-(2-(3,5-difluorophenyl)-1-(3-(1-methyl-1H-pyrazol-4-yl)pyridin-2-yl)ethyl)-2-(5-fluoro-1H-indol-3-yl)acetamide (**434**):

Prepared 1.5 mg of the title compound by a method analogous to **55F** using 3-fluoro-4-chlorophenylboronic acid and **55E**. MS (*m/z*) 538 [M+H]⁺.

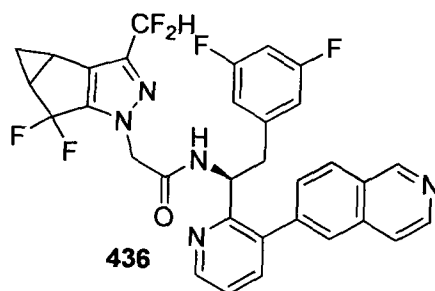
Example 435



Synthesis of (S)-N-(2-(3,5-difluorophenyl)-1-(3-(6-methoxynaphthalen-2-yl)pyridin-2-yl)ethyl)-2-(5-fluoro-1H-indol-3-yl)acetamide (**435**):

Prepared 37.1 mg of the title compound by a method analogous to **55F** using 6-methoxy-2-naphthaleneboronic acid and **55E**. MS (*m/z*) 566 [M+H]⁺.

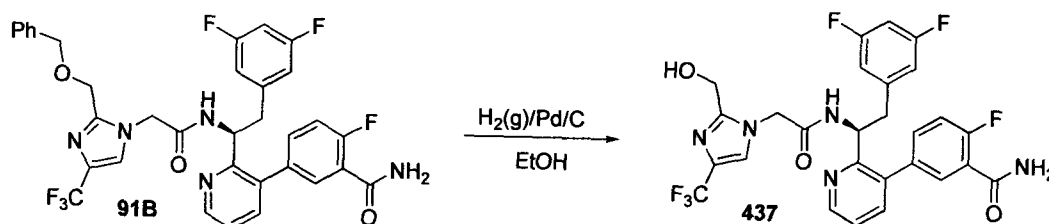
Example 436



Synthesis of (S)-N-(1-(3-(isoquinolin-6-yl)-pyridin-2-yl)-2-(3,5-difluorophenyl)ethyl)-2-(3-(difluoromethyl)-5,6-dihydro-4,5-(methano)-6,6-difluoro-cyclopenta[c]pyrazol-1(4H)-yl)acetamide (**436**):

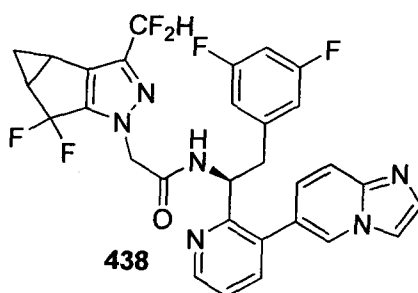
Prepared 15.1 mg of the title compound by a method analogous to **68B** using **68A** and
5 isoquinoline-6-ylboronic acid. MS (*m/z*) 608 [*M*+*H*]⁺.

Example 437



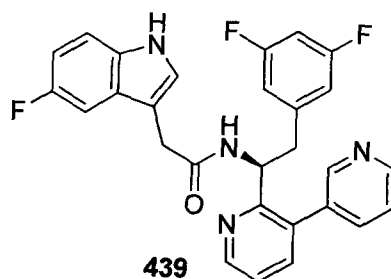
- 10 Synthesis of (S)-5-(2-(2-(3,5-difluorophenyl)-1-(2-(2-(hydroxymethyl)-4-(trifluoromethyl)-1H-imidazol-1-yl)acetamido)ethyl)pyridin-3-yl)-2-fluorobenzamide (**437**):
Dissolved 21.8 mg of **91B** in 1 ml EtOH. Added 10 mg of 10% Pd/C. Stirred at RT under 1 atm
H₂ for 72 hrs. Filtered reaction and purified filtrate by RP HPLC using a C18 column with a
gradient of 0.1%/H₂O, 0.1% TFA-acetonitrile to give 10.8 mg of the title compound. MS (*m/z*)
15 578 [*M*+*H*]⁺.

Example 428



- Synthesis of (S)-N-(1-(3-(imidazo[1,2-a]pyridine-6-yl)-pyridin-2-yl)-2-(3,5-difluorophenyl)ethyl)-2-(3-(difluoromethyl)-5,6-dihydro-4,5-(methano)-6,6-difluoro-cyclopenta[c]pyrazol-1(4H)-yl)acetamide (**438**):
Prepared 4.3 mg of the title compound by a method analogous to **68B** using **68A** and
imidazo[1,2-a]pyridine-6-boronic acid. MS (*m/z*) 597 [*M*+*H*]⁺.

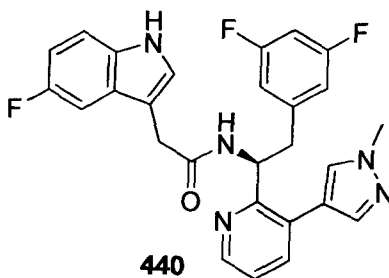
25 Example 439



Synthesis of (S)-N-(1-(3,3'-bipyridin-2-yl)-2-(3,5-difluorophenyl)ethyl)-2-(5-fluoro-1H-indol-3-yl)acetamide (**439**):

Prepared 20.8 mg of the title compound by a method analogous to **55F** using (pyridin-3-yl)boronic acid and **55E**. MS (*m/z*) 487 [M+H]⁺.

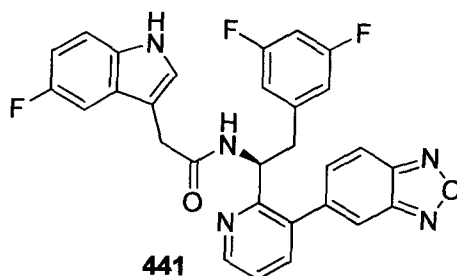
Example 440



Synthesis of (S)-N-(2-(3,5-difluorophenyl)-1-(3-(1-methyl-1H-pyrazol-4-yl)pyridin-2-yl)ethyl)-2-(5-fluoro-1H-indol-3-yl)acetamide (**440**):

Prepared 8.9 mg of the title compound by a method analogous to **55F** using 1-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole and **55E**. MS (*m/z*) 490 [M+H]⁺.

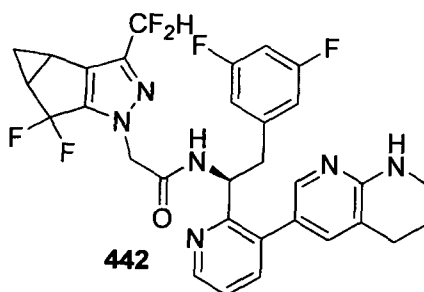
Example 441



Synthesis of (S)-N-(1-(3-(benzo[c][1,2,5]oxadiazol-5-yl)pyridin-2-yl)-2-(3,5-difluorophenyl)ethyl)-2-(5-fluoro-1H-indol-3-yl)acetamide (**441**):

Prepared 16 mg of the title compound by a method analogous to **55F** using benzo[c][1,2,5]oxadiazol-5-ylboronic acid and **55E**. MS (*m/z*) 528 [M+H]⁺.

Example 442

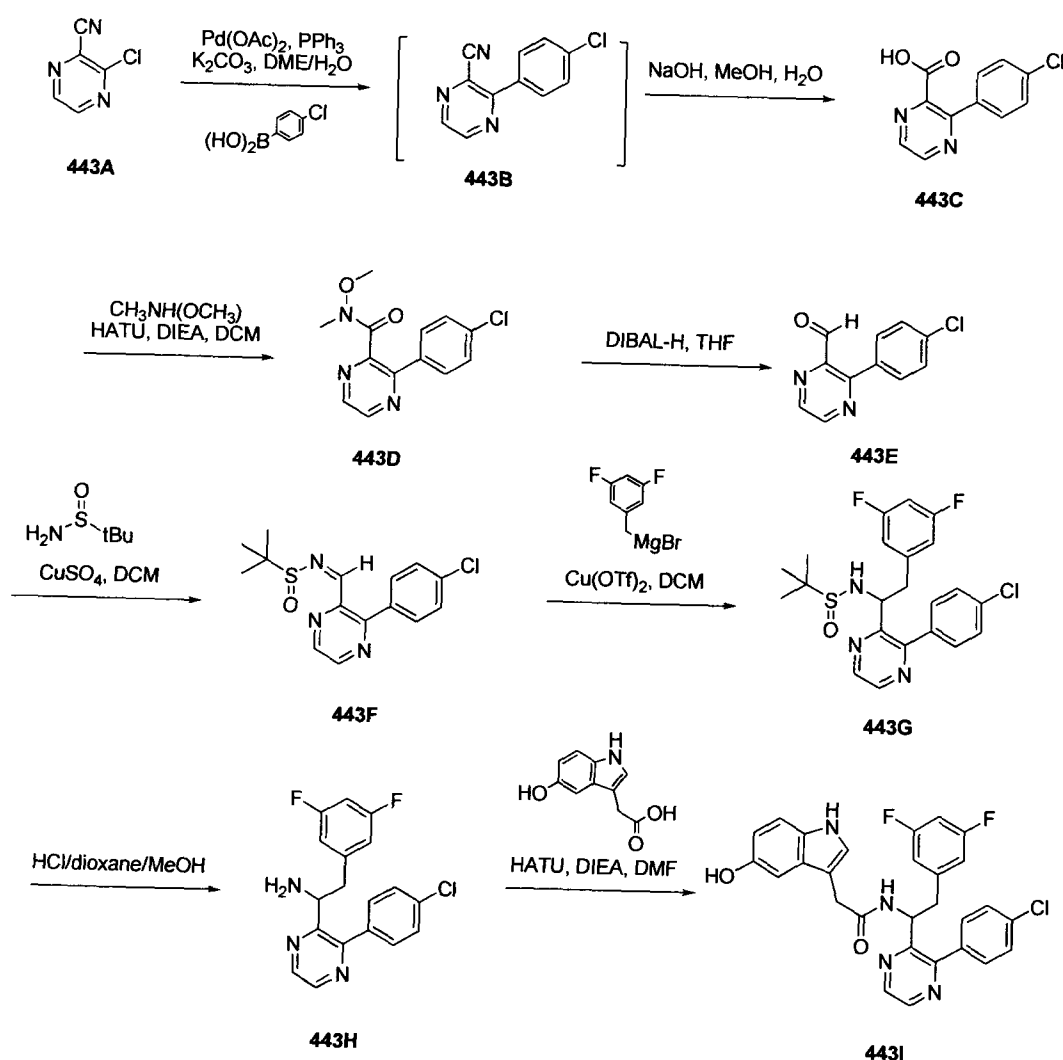


Synthesis of (S)-N-(1-(3-(5,6,7,8-tetrahydro-1,8-naphthyridin-3-yl)-pyridin-2-yl)-2-(3,5-difluorophenyl)ethyl)-2-(3-(difluoromethyl)-5,6-dihydro-4,5-(methano)-6,6-difluoro-

5 cyclopenta[c]pyrazol-1(4H)-yl)acetamide (**442**):

Prepared 1.2 mg of the title compound by a method analogous to **68B** using **68A** and (8-Pivaloyl-5,6,7,8-tetrahydro-1,8-naphthyridin-3-yl)boronic acid pinacol ester. MS (m/z) 613 $[M+H]^+$.

10 Example 443



Synthesis of 3-(4-chlorophenyl)pyrazine-2-carboxylic acid (**443C**):

To a solution of 3-chloropyrazine-2-carbonitrile (1.39 g, 10 mmol) in a mixture of DME (30 mL) and H_2O (15 mL) was added 4-chlorophenylboronic acid (1.56 g, 10 mmol) and K_2CO_3 (4.13 g, 30 mmol), $\text{Pd}(\text{OAc})_2$ (112 mg, 0.5 mmol) and triphenylphosphine (polymer-bound, 3.0 mmol). The reaction tube was sealed and heated at 95 °C overnight. After cooled to room temperature, the reaction mixture was poured into ethyl acetate and filtered through a pad of celite. The filtrate was concentrated to dryness and dissolved in 50 mL MeOH and 80 mL 4 N NaOH. The reaction was heated at 80 °C overnight. After cooled to room temperature, the mixture was acidified with concentrated HCl to pH = 1. After removing the volatile, the crude was used in the next step without further purification.

Synthesis of 3-(4-chlorophenyl)-N-methoxy-N-methylpyrazine-2-carboxamide (**443D**):

Example 443D was prepared according to the method presented for the synthesis of Example 13G utilizing crude of **443C** and N,O-dimethyl hydroxyamine hydrochloride to provide 3-(4-chlorophenyl)-N-methoxy-N-methylpyrazine-2-carboxamide: MS (m/z): 278.2 [M+H]⁺; ¹H NMR (400 MHz, cdcl₃) δ 8.69 (s, 1H), 8.55 (d, J = 2.1 Hz, 1H), 7.69 (d, J = 8.3 Hz, 2H), 7.44 (d, J = 8.4 Hz, 2H), 3.48 (s, 3H), 3.28 (s, 3H).

Synthesis of 3-(4-chlorophenyl)pyrazine-2-carbaldehyde (**443E**):

To a solution of 3-(4-chlorophenyl)-N-methoxy-N-methylpyrazine-2-carboxamide (670 mg, 2.4 mmol) in THF (5 mL) was added DIBAL-H (1.0 M/toluene, 4.8 mmol) at -10 °C. After stirred at -10 °C for 10 min, the reaction was poured into ethyl acetate and saturated NH₄Cl solution. The organic layer was separated and dried over sodium sulfate, filtered and concentrated. After removing the volatile, the crude was used in the next step without further purification. MS (m/z): 219.2 [M+H]⁺.

Synthesis of N-((3-(4-chlorophenyl)pyrazin-2-yl)methylene)-2-methylpropane-2-sulfinamide (**443F**):

To a solution of 3-(4-chlorophenyl)pyrazine-2-carbaldehyde (crude from above reaction) in DCM (5 mL) was added (S)- 2-methylpropane-2-sulfinamide (320 mg, 2.64 mmol) and CuSO₄ (766 mg, 4.8 mmol) at room temperature. After stirred at room temperature for 3 h, the reaction was filtered through a pad of celite and washed with DCM. The organic was dried over sodium sulfate, filtered and concentrated. After removing the volatile, the resulting residue was purified by silica gel chromatography eluting with EtOAc / hexanes to afford 0.48 g of the title product. MS (m/z): 321.8 [M+H]⁺.

Synthesis of N-(1-(3-(4-chlorophenyl)pyrazin-2-yl)-2-(3,5-difluorophenyl)ethyl)-2-methylpropane-2-sulfinamide (**443G**):

To a solution of N-((3-(4-chlorophenyl)pyrazin-2-yl)methylene)-2-methylpropane-2-sulfinamide (480 mg, 1.5 mmol) and Cu(OTf) (27 mg, 0.075 mmol) in DCM (5 mL) was added (3,5-difluorobenzyl)magnesium bromide (0.5 M in ether, 3.0 mmol) at room temperature. After stirred at room temperature for 1 h, the reaction was poured into ethyl acetate and saturated NH₄Cl solution. The organic layer was separated and dried over sodium sulfate, filtered and concentrated. After removing the volatile, the crude was used in the next step without further purification. MS (m/z): 449.8 [M+H]⁺.

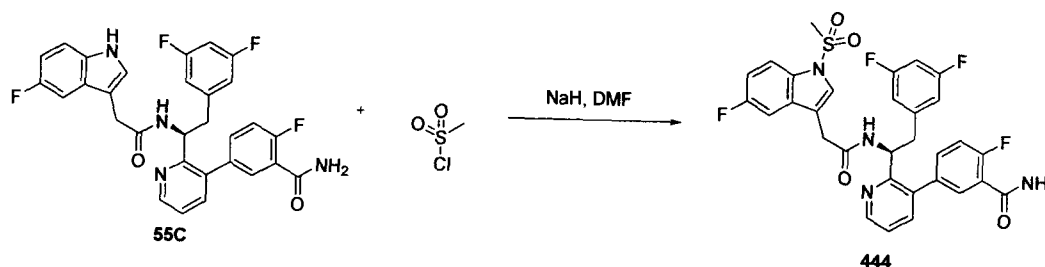
Synthesis of 1-(3-(4-chlorophenyl)pyrazin-2-yl)-2-(3,5-difluorophenyl)ethanamine (**443H**):

To a solution of N-(1-(3-(4-chlorophenyl)pyrazin-2-yl)-2-(3,5-difluorophenyl)ethyl)-2-methylpropane-2-sulfinamide (crude from above reaction) in MeOH (5 mL) was added 2 mL 4 N HCl in dioxane at room temperature. After stirred at room temperature overnight, the volatile was removed in vacuo and the crude was used in the next step without further purification. MS (m/z): 346.1 [M+H]⁺.

Synthesis of N-(1-(3-(4-chlorophenyl)pyrazin-2-yl)-2-(3,5-difluorophenyl)ethyl)-2-(5-hydroxy-1H-indol-3-yl)acetamide (**443I**):

Example 443I was prepared (10.3 mg) according to the method presented for the synthesis of Example 13G utilizing **443H** and 2-(5-hydroxy-1H-indol-3-yl)acetic acid to provide (S)-5-(2-(1-(2-(5-bromo-1H-indol-3-yl)acetamido)-2-(3,5-difluorophenyl)ethyl)pyridin-3-yl)-2-fluorobenzamide: MS (m/z): 520.0 [M+H]⁺; ¹H NMR (400 MHz, dmsO) δ 10.47 (s, 1H), 8.74 – 8.63 (m, 2H), 8.59 (s, 1H), 7.40 (s, 4H), 7.07 (d, J = 8.6 Hz, 1H), 6.92 (d, J = 15.6 Hz, 2H), 6.78 (s, 1H), 6.55 (d, J = 8.3 Hz, 1H), 6.41 (d, J = 7.1 Hz, 2H), 5.25 (q, J = 7.5 Hz, 1H), 3.41 (s, 2H), 3.04 (dd, J = 12.9, 6.9 Hz, 1H), 3.01 – 2.87 (m, 1H).

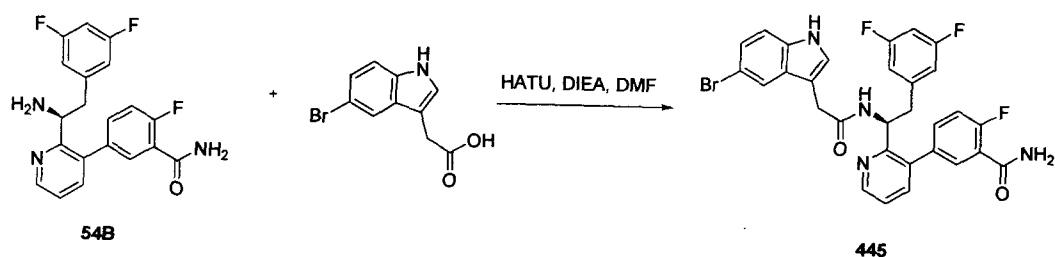
Example 444



Synthesis of (S)-5-(2-(2-(3,5-difluorophenyl)-1-(2-(5-fluoro-1-(methylsulfonyl)-1H-indol-3-yl)acetamido)ethyl)pyridin-3-yl)-2-fluorobenzamide (**444**):

To a solution of (S)-5-(2-(2-(3,5-difluorophenyl)-1-(2-(5-fluoro-1H-indol-3-yl)acetamido)ethyl)pyridin-3-yl)-2-fluorobenzamide (10 mg, 0.02 mmol) in DMF (1 mL) was added NaH (1.6 mg, 0.04 mmol) and methylsulfonyl chloride (23 mg, 0.2 mmol). The reaction was stirred at room temperature overnight and was then purified by reverse phase HPLC eluting with acetonitrile/water to afford 1.0 mg of the title compound. MS (m/z): 625.1 [M+H]⁺; HPLC retention time 3.74 min (2-98% acetonitrile: water with 0.05% trifluoroacetic acid).

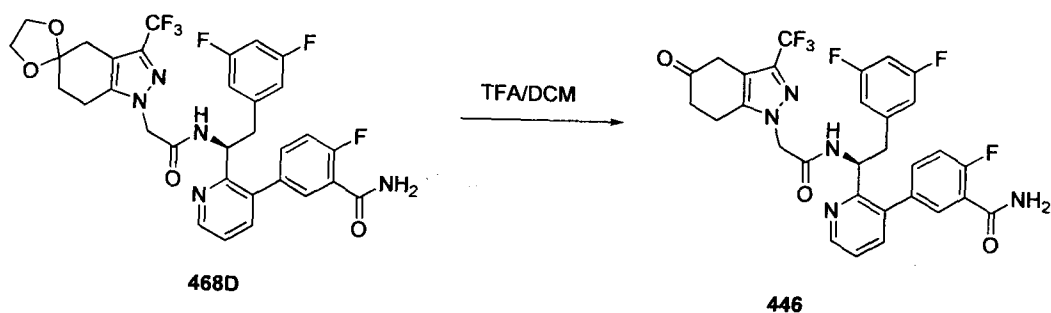
Example 445



Synthesis of (S)-5-(2-(1-(2-(5-bromo-1H-indol-3-yl)acetamido)-2-(3,5-difluorophenyl)ethyl)pyridin-3-yl)-2-fluorobenzamide (**445**):

Example 445 was prepared (5.7 mg) according to the method presented for the synthesis of Example 13G utilizing **54B** and 2-(5-bromo-1H-indol-3-yl)acetic acid to provide (S)-5-(2-(1-(2-(5-bromo-1H-indol-3-yl)acetamido)-2-(3,5-difluorophenyl)ethyl)pyridin-3-yl)-2-fluorobenzamide: MS (m/z): 607.2 [M+H]⁺; HPLC retention time 3.62 min (2-98% acetonitrile: water with 0.05% trifluoroacetic acid). ¹H NMR (400 MHz, cdcl₃) δ 8.51 (d, J = 7.4 Hz, 1H), 8.40 (d, J = 5.5 Hz, 1H), 8.26 (s, 1H), 7.90 (t, J = 29.1 Hz, 1H), 7.81 (s, 1H), 7.61 (dd, J = 17.6, 9.9 Hz, 2H), 7.34 – 7.21 (m, 1H), 7.21 – 7.06 (m, 3H), 6.93 (d, J = 8.6 Hz, 1H), 6.49 (t, J = 7.7 Hz, 2H), 6.11 (d, J = 5.9 Hz, 2H), 5.33 (q, J = 7.9 Hz, 1H), 3.65 (dd, J = 22.0, 14.7 Hz, 1H), 3.53 (d, J = 15.8 Hz, 1H), 3.03 (dd, J = 13.6, 7.7 Hz, 1H), 2.96 – 2.82 (m, 1H).

Example 446

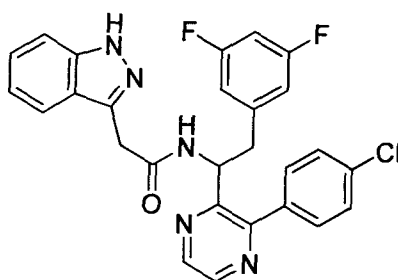


Synthesis of (S)-5-(2-(2-(3,5-difluorophenyl)-1-(2-(5-oxo-3-(trifluoromethyl)-4,5,6,7-tetrahydro-1H-indazol-1-yl)acetamido)ethyl)pyridin-3-yl)-2-fluorobenzamide (**446**):

A solution of (S)-5-(2-(2-(3,5-difluorophenyl)-1-(2-(3'-(trifluoromethyl)-6',7'-dihydrospiro[[1,3]dioxolane-2,5'-indazole]-1'(4'H)-yl)acetamido)ethyl)pyridin-3-yl)-2-fluorobenzamide (320 mg, 0.48 mmol) in 3 mL DCM and 1 mL TFA was stirred at room temperature overnight. The volatile was removed in vacuo and the residue was then purified by reverse phase HPLC eluting with acetonitrile/water to afford 11.8 mg of the title compound.:

MS (m/z): 616.7 [M+H]⁺; HPLC retention time 0.94 min (2-98% acetonitrile: water with 0.05% trifluoroacetic acid). ¹H NMR (400 MHz, cd₃od) δ 8.76 – 8.67 (m, 1H), 7.68 (dd, J = 7.8, 1.6 Hz, 1H), 7.57 – 7.46 (m, 2H), 7.32 (s, 1H), 7.22 (m, 1H), 6.68 (t, J = 9.2 Hz, 1H), 6.34 (d, J = 6.2 Hz, 2H), 5.36 (t, J = 7.6 Hz, 1H), 4.93 – 4.76 (m, 2H), 3.29 (dt, J = 3.2, 1.6 Hz, 1H), 3.06 (d, J = 7.5 Hz, 1H), 2.85 (d, J = 46.2 Hz, 2H), 2.77 – 2.62 (m, 2H), 2.60 – 2.42 (m, 2H), 1.98 (dt, J = 31.8, 11.5 Hz, 2H).

Example 447



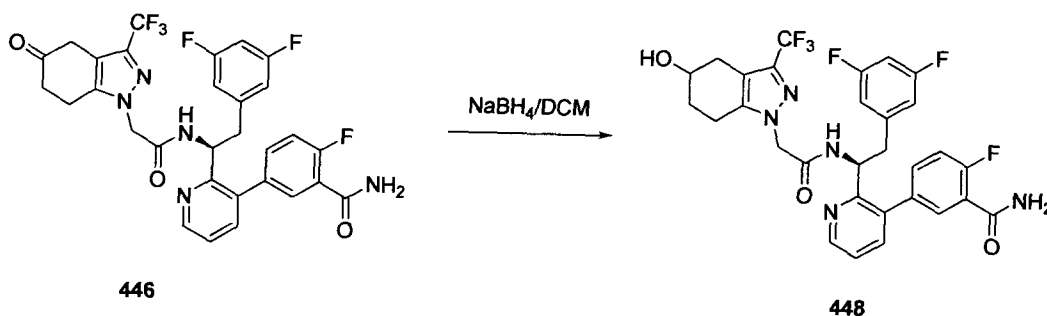
447

Synthesis of N-(1-(3-(4-chlorophenyl)pyrazin-2-yl)-2-(3,5-difluorophenyl)ethyl)-2-(1H-indazol-3-yl)acetamide (**447**):

Example 447 was prepared (5.4 mg) according to the method presented for the synthesis of Example 13G utilizing **443H** and 2-(1H-indazol-3-yl)acetic acid to provide N-(1-(3-(4-

chlorophenyl)pyrazin-2-yl)-2-(3,5-difluorophenyl)ethyl)-2-(1H-indazol-3-yl)acetamide: MS (m/z): 505.1 [M+H]⁺; ¹H NMR (400 MHz, dmso) δ 9.06 (d, J = 7.4 Hz, 1H), 8.75 (s, 1H), 8.62 (s, 1H), 7.50 – 7.36 (m, 5H), 7.26 (t, J = 7.6 Hz, 1H), 6.99 (dt, J = 14.9, 7.8 Hz, 3H), 6.51 (d, J = 6.9 Hz, 2H), 5.26 (d, J = 7.2 Hz, 1H), 3.83 – 3.68 (m, 2H), 3.15 – 2.93 (m, 2H).

Example 448



446

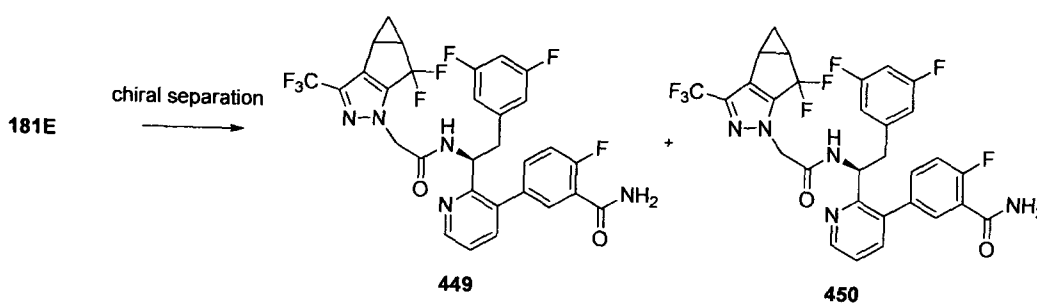
448

Synthesis of 5-(2-((1S)-2-(3,5-difluorophenyl)-1-(2-(5-hydroxy-3-(trifluoromethyl)-4,5,6,7-tetrahydro-1H-indazol-1-yl)acetamido)ethyl)pyridin-3-yl)-2-fluorobenzamide (**448**):

To solution of (S)-5-(2-(2-(3,5-difluorophenyl)-1-(2-(5-oxo-3-(trifluoromethyl)-4,5,6,7-tetrahydro-1H-indazol-1-yl)acetamido)ethyl)pyridin-3-yl)-2-fluorobenzamide (24 mg, 0.04 mmol) in 1 mL DCM was added NaBH₄ (200 mg, 5.3 mmol) and the resulting solution was stirred at room temperature overnight. The reaction was poured into ethyl acetate and washed with saturated NH₄Cl solution and brine. The organic layer was dried over sodium sulfate, filtered and concentrated. The resulting residue was purified by reverse phase HPLC eluting with acetonitrile/water to afford 10.8 mg of the title compound.: MS (m/z): 618.3 [M+H]⁺; ¹H

NMR of mixture of diastereomers (400 MHz, cdcl₃) δ 9.31 (d, J = 7.3 Hz, 1H), 8.75 (s, 1H), 7.99 – 7.88 (m, 1H), 7.80 – 7.58 (m, 2H), 7.50 (s, 1H), 7.34 – 7.22 (m, 1H), 6.98 (m, 1H), 6.61 (t, J = 8.6 Hz, 1H), 6.45 (s, 1H), 6.21 (s, 2H), 5.57 – 5.40 (m, 1H), 4.89 – 4.61 (m, 2H), 3.15 (dd, J = 13.5, 7.0 Hz, 1H), 3.10 – 2.95 (m, 1H), 2.88 (d, J = 12.2 Hz, 1H), 2.70 (m, 2H), 2.55 (dd, J = 38.9, 32.9 Hz, 1H), 2.01 (m, 1H), 1.91 (m, 1H).

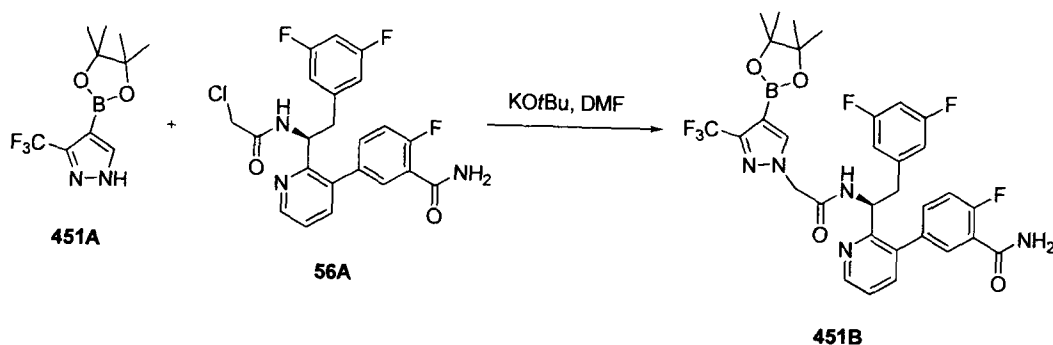
Example 449 and 450



Synthesis of 5-(2-((1S)-1-(2-(5,5-difluoro-3-(trifluoromethyl)-3b,4,4a,5-tetrahydro-1H-cyclopropa[3,4]cyclopenta[1,2-c]pyrazol-1-yl)acetamido)-2-(3,5-difluorophenyl)ethyl)pyridin-3-yl)-2-fluorobenzamide (**449**) and 5-(2-((1S)-1-(2-(5,5-difluoro-3-(trifluoromethyl)-3b,4,4a,5-tetrahydro-1H-cyclopropa[3,4]cyclopenta[1,2-c]pyrazol-1-yl)acetamido)-2-(3,5-difluorophenyl)ethyl)pyridin-3-yl)-2-fluorobenzamide (**450**):

The two diastereomers of **181E** were separated by chiral HPLC (Chiralpak AD-H, Heptane:IPA 70:30) to provide **449** (18 mg, fast eluting peak) and **450** (18 mg, slow eluting peak). MS (m/z): 636.4 [M+H]⁺.

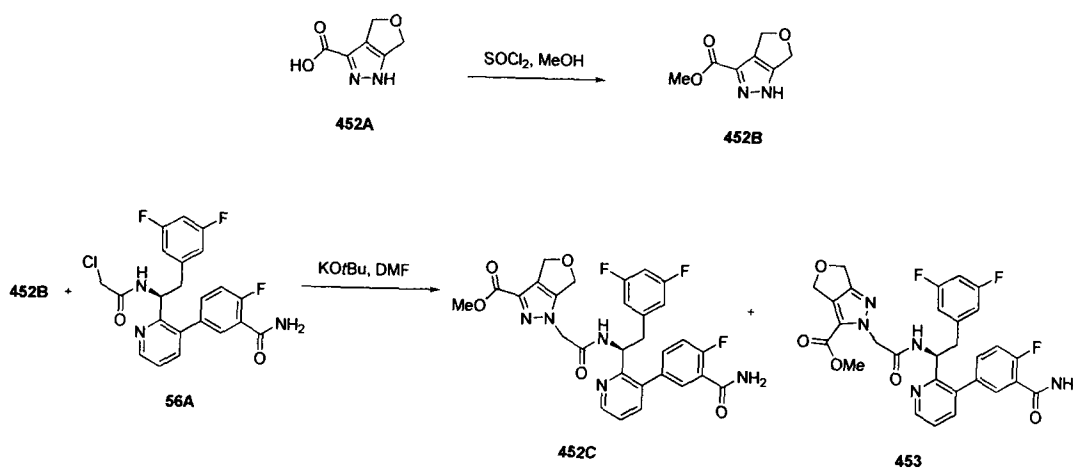
Example 451



Synthesis of (S)-5-(2-(2-(3,5-difluorophenyl)-1-(2-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3-(trifluoromethyl)-1H-pyrazol-1-yl)acetamido)ethyl)pyridin-3-yl)-2-fluorobenzamide (**451B**):

Example 451B was prepared (6.6 mg) according to the method presented for the synthesis of Example 58D utilizing **56A** and 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3-(trifluoromethyl)-1H-pyrazole to provide (S)-5-(2-(2-(3,5-difluorophenyl)-1-(2-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3-(trifluoromethyl)-1H-pyrazol-1-yl)acetamido)ethyl)pyridin-3-yl)-2-fluorobenzamide: MS (m/z): 674.1 [M+H]⁺; ¹H NMR (400 MHz, cdcl₃) δ 8.57 (d, J = 4.9 Hz, 1H), 7.79 (s, 1H), 7.56 (d, J = 7.3 Hz, 1H), 7.47 (d, J = 8.0 Hz, 1H), 7.38 – 7.22 (m, 1H), 7.21 – 7.11 (m, 1H), 6.78 (s, 1H), 6.53 (t, J = 9.0 Hz, 1H), 6.09 (d, J = 6.0 Hz, 2H), 5.82 (s, 1H), 5.42 (dd, J = 14.3, 8.4 Hz, 1H), 4.83 (s, 2H), 2.95 – 2.72 (m, 2H), 1.35 – 1.20 (m, 12H).

Example 452 and 453



Synthesis of methyl 4,6-dihydro-1H-furo[3,4-c]pyrazole-3-carboxylate (**452B**):

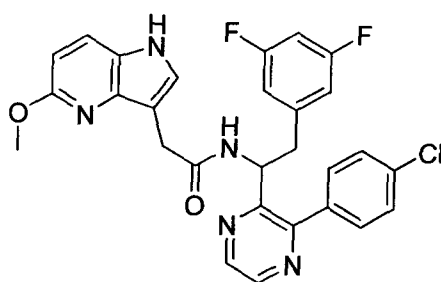
Example 452B was prepared according to the method presented for the synthesis of Example 55C utilizing 4,6-dihydro-1H-furo[3,4-c]pyrazole-3-carboxylic acid to provide the title compound: MS (m/z):169.1 [M+H]⁺.

5 Synthesis of (S)-methyl 1-(2-((1-(3-(3-carbamoyl-4-fluorophenyl)pyridin-2-yl)-2-(3,5-difluorophenyl)ethyl)amino)-2-oxoethyl)-4,6-dihydro-1H-furo[3,4-c]pyrazole-3-carboxylate (**452C**) and (S)-methyl 2-(2-((1-(3-(3-carbamoyl-4-fluorophenyl)pyridin-2-yl)-2-(3,5-difluorophenyl)ethyl)amino)-2-oxoethyl)-4,6-dihydro-2H-furo[3,4-c]pyrazole-3-carboxylate (**453**):

10 Example 452C (2.4 mg) and 453 (2.7 mg) were prepared according to the method presented for the synthesis of Example 58D utilizing **56A** and methyl 4,6-dihydro-1H-furo[3,4-c]pyrazole-3-carboxylate to provide (S)-methyl 1-(2-(1-(3-(3-carbamoyl-4-fluorophenyl)pyridin-2-yl)-2-(3,5-difluorophenyl)ethylamino)-2-oxoethyl)-4,6-dihydro-1H-furo[3,4-c]pyrazole-3-carboxylate: MS (m/z): 580.4 [M+H]⁺; ¹H NMR (400 MHz, cdcl₃) δ 9.58 (s, 1H), 8.78 (d, J = 4.8 Hz, 1H), 7.93 (d, J = 6.7 Hz, 1H), 7.79 – 7.62 (m, 2H), 7.58 (s, 1H), 7.33 – 7.22 (m, 2H), 6.86 (s, 1H), 6.61 (s, 1H), 6.35 (s, 1H), 6.18 (d, J = 5.9 Hz, 2H), 5.46 (s, 1H), 5.00 (s, 2H), 4.92 – 4.69 (m, 4H), 3.87 (s, 3H), 3.07 – 2.80 (m, 1H), 3.07 – 2.81 (m, 1H) and (S)-methyl 2-(2-(1-(3-(3-carbamoyl-4-fluorophenyl)pyridin-2-yl)-2-(3,5-difluorophenyl)ethylamino)-2-oxoethyl)-4,6-dihydro-2H-furo[3,4-c]pyrazole-3-carboxylate: MS (m/z): 580.7 [M+H]⁺.

20

Example 454



454

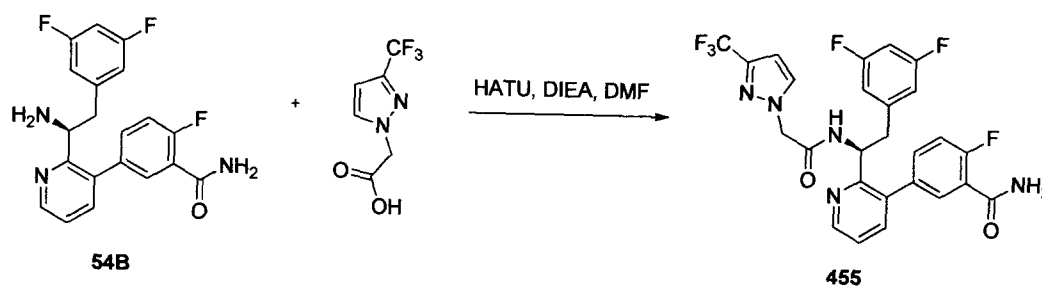
25 Synthesis of N-(1-(3-(4-chlorophenyl)pyrazin-2-yl)-2-(3,5-difluorophenyl)ethyl)-2-(5-methoxy-1H-pyrrolo[3,2-b]pyridin-3-yl)acetamide (**454**):

Example 454 was prepared (4.2 mg) according to the method presented for the synthesis of Example 13G utilizing **443H** and 2-(5-methoxy-1H-pyrrolo[3,2-b]pyridin-3-yl)acetic acid to provide N-(1-(3-(4-chlorophenyl)pyrazin-2-yl)-2-(3,5-difluorophenyl)ethyl)-2-(5-methoxy-1H-

pyrrolo[3,2-b]pyridin-3-yl)acetamide: MS (m/z): 535.1 $[M+H]^+$; 1H NMR (400 MHz, dmso) δ 11.08 (s, 1H), 8.68 (d, $J = 8.2$ Hz, 2H), 8.62 (s, 1H), 7.73 (s, 1H), 7.50 – 7.39 (m, 4H), 7.28 (s, 1H), 6.91 (t, $J = 9.1$ Hz, 1H), 6.59 (d, $J = 8.8$ Hz, 1H), 6.38 (d, $J = 6.6$ Hz, 2H), 5.32 (d, $J = 7.5$ Hz, 1H), 3.86 (s, 3H), 3.58 – 3.31 (m, 2H), 2.97 (m, 2H).

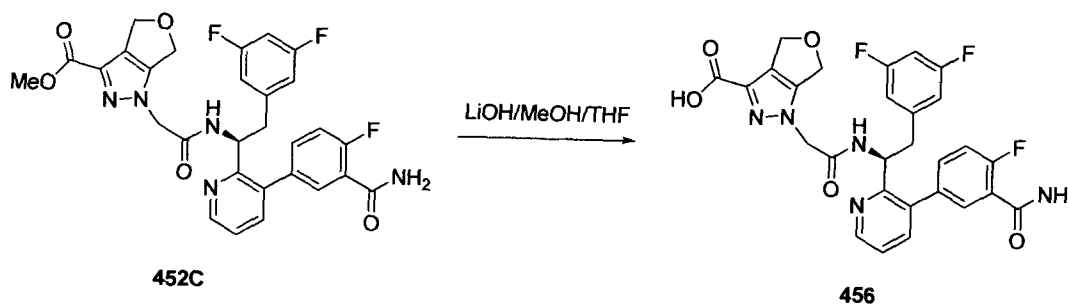
5

Example 455



- 10 Synthesis of (S)-5-(2-(2-(3,5-difluorophenyl)-1-(2-(3-(trifluoromethyl)-1H-pyrazol-1-yl)acetamido)ethyl)pyridin-3-yl)-2-fluorobenzamide (**455**):
- Example 455 was prepared (55 mg) according to the method presented for the synthesis of Example 13G utilizing **54B** and 2-(3-(trifluoromethyl)-1H-pyrazol-1-yl)acetic acid to provide (S)-5-(2-(2-(3,5-difluorophenyl)-1-(2-(3-(trifluoromethyl)-1H-pyrazol-1-yl)acetamido)ethyl)pyridin-3-yl)-2-fluorobenzamide: MS (m/z): 548.1 $[M+H]^+$; HPLC retention time 3.56 min (2-98% acetonitrile: water with 0.05% trifluoroacetic acid). 1H NMR (400 MHz, $cdCl_3$) δ 9.53 (d, $J = 7.1$ Hz, 1H), 8.79 (d, $J = 5.5$ Hz, 1H), 7.98 (d, $J = 7.9$ Hz, 1H), 7.93 – 7.70 (m, 2H), 7.62 (s, 1H), 7.60 (d, $J = 6.5$ Hz, 1H), 7.62 – 7.23 (m, 2H), 6.95 (d, $J = 10.2$ Hz, 1H), 6.61 (dd, $J = 19.8, 11.5$ Hz, 3H), 6.20 (d, $J = 6.1$ Hz, 2H), 5.48 (q, $J = 7.6$ Hz, 1H), 5.00 – 4.84 (m, 2H), 3.18 (dd, $J = 13.5, 6.8$ Hz, 1H), 3.02 (dd, $J = 13.6, 9.0$ Hz, 1H).
- 15
- 20

Example 456

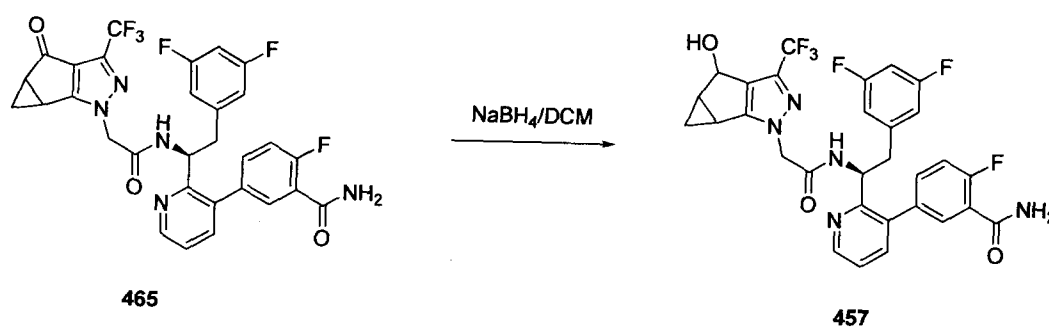


25

Synthesis of (S)-1-(2-(1-(3-(3-carbamoyl-4-fluorophenyl)pyridin-2-yl)-2-(3,5-difluorophenyl)ethylamino)-2-oxoethyl)-4,6-dihydro-1H-furo[3,4-c]pyrazole-3-carboxylic acid (**456**):

The carboxylic acid **456** was prepared (4.6 mg) according to the method presented for the synthesis of Example 60G utilizing **452C** as starting material to provide (S)-1-(2-(1-(3-(3-carbamoyl-4-fluorophenyl)pyridin-2-yl)-2-(3,5-difluorophenyl)ethylamino)-2-oxoethyl)-4,6-dihydro-1H-furo[3,4-c]pyrazole-3-carboxylic acid: MS (m/z): 566.3 [M+H]⁺. ¹H NMR (400 MHz, cdcl₃) δ 8.83 (d, J = 4.0 Hz, 1H), 7.88 (d, J = 6.9 Hz, 1H), 7.66 (dd, J = 21.3, 15.7 Hz, 1H), 7.60 – 7.58 (m, 1H), 7.24 (m, 2H), 6.98 (m, 1H), 6.68 (s, 1H), 6.57 (s, 1H), 6.16 (d, J = 5.7 Hz, 3H), 5.45 (s, 1H), 5.25 (d, J = 4.3 Hz, 2H), 4.97 (s, 2H), 4.85 (s, 2H), 3.13 (d, J = 46.3 Hz, 1H), 3.05 (m, 1H).

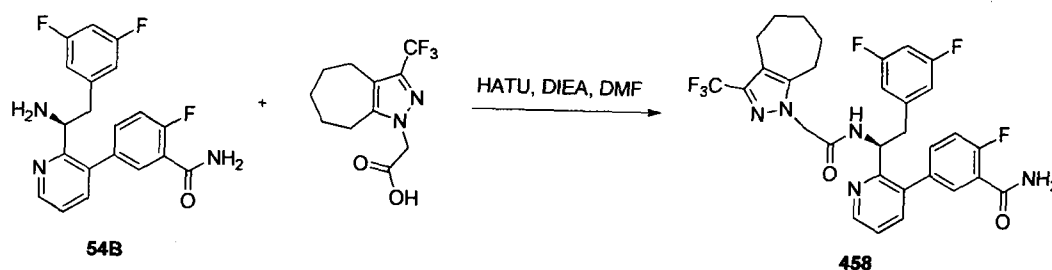
Example 457



Synthesis of 5-(2-((1S)-2-(3,5-difluorophenyl)-1-(2-(4-hydroxy-3-(trifluoromethyl)-4,4a,5,5a-tetrahydro-1H-cyclopropa[4,5]cyclopenta[1,2-c]pyrazol-1-yl)acetamido)ethyl)pyridin-3-yl)-2-fluorobenzamide (**457**):

The example **457** was prepared (2.6 mg) according to the method presented for the synthesis of Example 448 utilizing **465** as starting material: MS (m/z): 616.1 [M+H]⁺.

Example 458

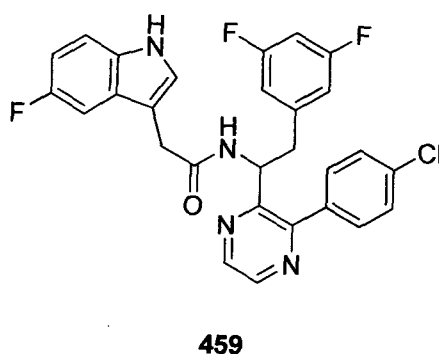


Synthesis of (S)-5-(2-(2-(3,5-difluorophenyl)-1-(2-(3-(trifluoromethyl)-5,6,7,8-tetrahydrocyclohepta[c]pyrazol-1(4H)-yl)acetamido)ethyl)pyridin-3-yl)-2-fluorobenzamide (458):

Example 458 was prepared (22 mg) according to the method presented for the synthesis of Example 13G utilizing **54B** and 2-(3-(trifluoromethyl)-5,6,7,8-tetrahydrocyclohepta[c]pyrazol-1(4H)-yl)acetic acid to provide (S)-5-(2-(2-(3,5-difluorophenyl)-1-(2-(3-(trifluoromethyl)-5,6,7,8-tetrahydrocyclohepta[c]pyrazol-1(4H)-yl)acetamido)ethyl)pyridin-3-yl)-2-

fluorobenzamide: MS (m/z): 616.6 [M+H]⁺; HPLC retention time 1.31 min (2-98% acetonitrile: water with 0.05% trifluoroacetic acid). ¹H NMR (400 MHz, cdcl₃) δ 9.37 (d, J = 7.5 Hz, 1H), 8.79 – 8.70 (m, 1H), 7.96 – 7.90 (m, 1H), 7.90 – 7.32 (m, 3H), 7.33 – 7.22 (m, 1H), 6.96 (d, J = 10.7 Hz, 1H), 6.61 (t, J = 5.6 Hz, 2H), 6.19 (d, J = 5.7 Hz, 2H), 5.47 (dd, J = 16.0, 7.5 Hz, 1H), 4.92 – 4.70 (m, 2H), 3.15 (dd, J = 13.5, 6.9 Hz, 1H), 3.06 – 2.91 (m, 1H), 2.91 – 2.86 (m, 1H), 2.69 – 2.40 (m, 4H), 1.80 (d, J = 5.1 Hz, 2H), 1.71 – 1.43 (m, 4H), 1.39 (dd, J = 13.0, 6.7 Hz, 1H).

Example 459

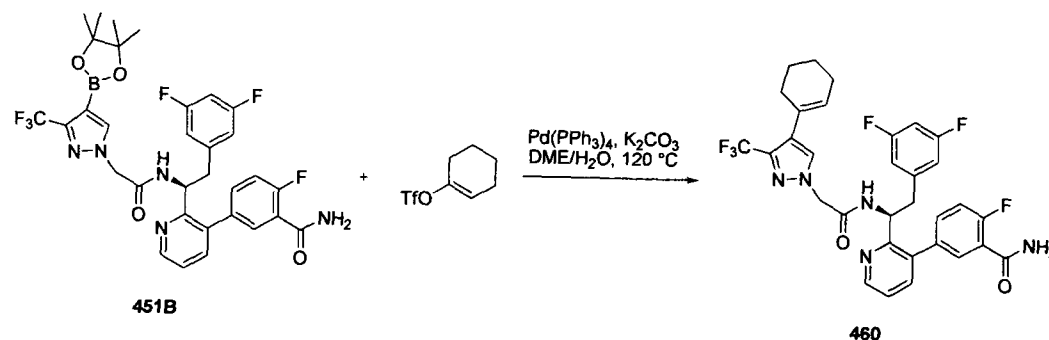


459

Synthesis of N-(1-(3-(4-chlorophenyl)pyrazin-2-yl)-2-(3,5-difluorophenyl)ethyl)-2-(5-fluoro-1H-indol-3-yl)acetamide (459):

Example 459 was prepared (11.3 mg) according to the method presented for the synthesis of Example 13G utilizing **443H** and 2-(5-fluoro-1H-indol-3-yl)acetic acid to provide N-(1-(3-(4-chlorophenyl)pyrazin-2-yl)-2-(3,5-difluorophenyl)ethyl)-2-(5-fluoro-1H-indol-3-yl)acetamide: MS (m/z): 522.2 [M+H]⁺; ¹H NMR (400 MHz, dmsO) δ 10.89 (s, 1H), 8.84 (d, J = 7.8 Hz, 1H), 8.70 (s, 1H), 8.61 (s, 1H), 7.43 (s, 4H), 7.26 (dd, J = 8.9, 4.5 Hz, 1H), 7.13 (d, J = 10.9 Hz, 2H), 6.88 (dt, J = 17.2, 9.0 Hz, 2H), 6.47 (d, J = 7.2 Hz, 2H), 5.25 (d, J = 7.6 Hz, 1H), 3.46 (s, 2H), 3.13 – 2.90 (m, 2H).

Example 460

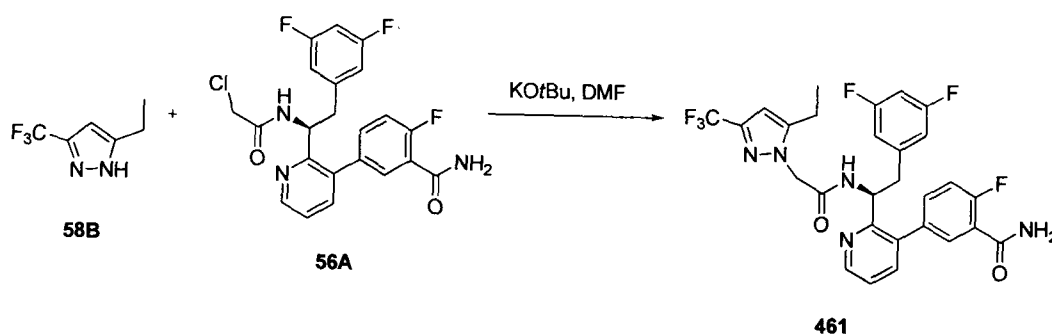


Synthesis of (S)-5-(2-(1-(2-(4-cyclohexenyl-3-(trifluoromethyl)-1H-pyrazol-1-yl)acetamido)-2-(3,5-difluorophenyl)ethyl)pyridin-3-yl)-2-fluorobenzamide (**460**):

Example 460 was prepared (4.9 mg) according to the method presented for the synthesis of

Example 55F utilizing **451B** and cyclohexenyl trifluoromethanesulfonate to provide (S)-5-(2-(1-(2-(4-cyclohexenyl-3-(trifluoromethyl)-1H-pyrazol-1-yl)acetamido)-2-(3,5-difluorophenyl)ethyl)pyridin-3-yl)-2-fluorobenzamide: MS (m/z): 628.3 [M+H]⁺; HPLC retention time 1.26 min (2-98% acetonitrile: water with 0.05% trifluoroacetic acid). ¹H NMR (400 MHz, cdCl₃) δ 9.25 (s, 1H), 8.77 (s, 1H), 8.02 (d, J = 8.3 Hz, 1H), 7.80 (m, 2H), 7.51 (d, J = 10.6 Hz, 1H), 7.41 – 7.22 (m, 2H), 6.93 (s, 1H), 6.66 – 6.63 (m, 1H), 6.59 (d, J = 22.3 Hz, 1H), 6.18 (d, J = 5.4 Hz, 2H), 5.88 (s, 1H), 5.51 (s, 1H), 4.88 (d, J = 9.5 Hz, 2H), 3.22 (m, 1H), 3.14 (m, 1H), 2.16 (m, 4H), 1.73 – 1.58 (m, 4H).

Example 461

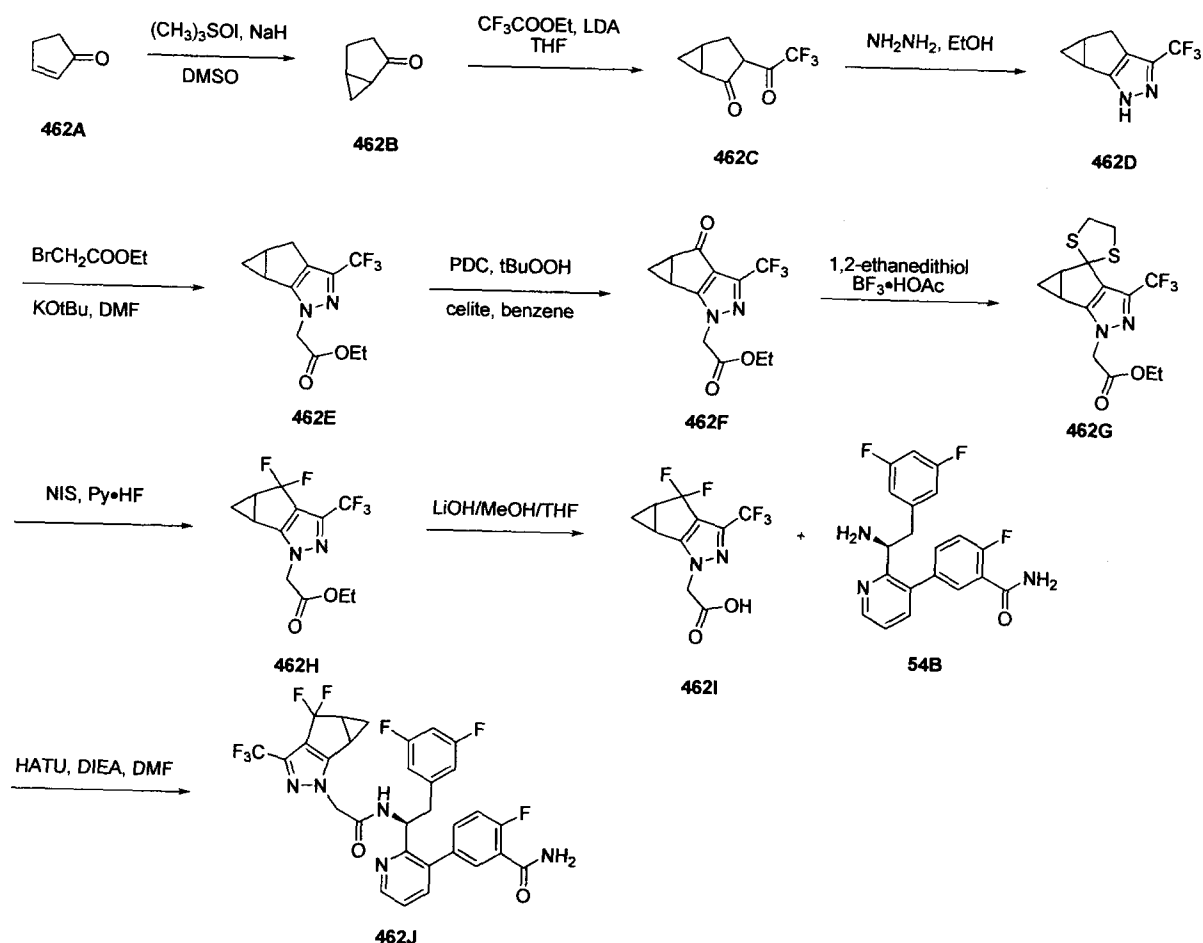


Synthesis of (S)-5-(2-(2-(3,5-difluorophenyl)-1-(2-(5-ethyl-3-(trifluoromethyl)-1H-pyrazol-1-yl)acetamido)ethyl)pyridin-3-yl)-2-fluorobenzamide (**461**):

Example 461 was prepared (24 mg) according to the method presented for the synthesis of

- 5 Example 58D utilizing **56A** and **58B** to provide (S)-5-(2-(2-(3,5-difluorophenyl)-1-(2-(5-ethyl-3-(trifluoromethyl)-1H-pyrazol-1-yl)acetamido)ethyl)pyridin-3-yl)-2-fluorobenzamide: MS (m/z): 576.2 [M+H]⁺; ¹H NMR (400 MHz, cdcl₃) δ 9.39 (d, J = 7.6 Hz, 1H), 8.76 (d, J = 5.4 Hz, 1H), 7.88 (m, 1H), 7.79 (s, 1H), 7.84 – 7.57 (m, 2H), 7.29 (d, J = 8.5 Hz, 1H), 7.27 – 7.21 (m, 1H), 6.95 (d, J = 9.6 Hz, 1H), 6.67 – 6.38 (m, 2H), 6.33 (s, 1H), 6.19 (d, J = 5.8 Hz, 2H), 5.48 (dd, J = 16.2, 7.6 Hz, 1H), 4.82 (q, J = 16.7 Hz, 2H), 3.23 – 3.02 (m, 1H), 3.02 – 2.78 (m, 1H), 2.50 (dd, J = 14.9, 7.5 Hz, 2H), 1.23 (t, J = 7.5 Hz, 3H).

Example 462



Synthesis of bicyclo[3.1.0]hexan-2-one (462B):

To a solution of trimethylsulfoxonium iodide (12.1 g, 55 mmol) in DMSO (50 mL) was added NaH (2.2 g, 55 mmol) in an ice-water bath. The solution was stirred at room temperature for 10 min and then cyclopent-2-enone (4.1 g, 50 mmol) was added. The reaction was stirred at room temperature for 1 h and was then poured into ether. The organic was washed with 5% LiCl and dried over sodium sulfate, filtered and concentrated. The resulting residue was purified by silica gel chromatography eluting with EtOAc / hexanes to afford 2.5 g of the title product. $R_f = 0.15$ (9:1 hexanes: EtOAc).

Synthesis of 3-(2,2,2-trifluoroacetyl)bicyclo[3.1.0]hexan-2-one (462C):

Example 462C was prepared according to the method presented for the synthesis of Example 60B utilizing bicyclo[3.1.0]hexan-2-one and trifluoroethyl acetate to provide 3-(2,2,2-trifluoroacetyl)bicyclo[3.1.0]hexan-2-one as a red oil: MS (m/z): 196.0 $[M+H]^+$.

Synthesis of 3-(trifluoromethyl)-4,4a,5,5a-tetrahydro-1H-cyclopropa[4,5]cyclopenta[1,2-c]pyrazole (462D):

Example 462D was prepared according to the method presented for the synthesis of Example 58B utilizing 3-(2,2,2-trifluoroacetyl)bicyclo[3.1.0]hexan-2-one and hydrazine hydrate to provide the title compound: MS (m/z):189.1 [M+H]⁺.

5 Synthesis of ethyl 2-(3-(trifluoromethyl)-4,4a,5,5a-tetrahydro-1H-cyclopropa[4,5]cyclopenta[1,2-c]pyrazol-1-yl)acetate (**462E**):

Example 462E was prepared according to the method presented for the synthesis of Example 58D utilizing **462D** and ethyl 2-bromoacetate to provide the title compound: MS (m/z):275.1 [M+H]⁺.

10

Synthesis of ethyl 2-(4-oxo-3-(trifluoromethyl)-4,4a,5,5a-tetrahydro-1H-cyclopropa[4,5]cyclopenta[1,2-c]pyrazol-1-yl)acetate (**462F**):

Example 462F was prepared according to the method presented for the synthesis of Example 60D utilizing **462E** to provide the title compound: MS (m/z):275.1 [M+H]⁺.

15

Synthesis of ethyl 2-(3-(trifluoromethyl)-5,5a-dihydrospiro[cyclopropa[4,5]cyclopenta[1,2-c]pyrazole-4,2'-[1,3]dithiolan]-1(4aH)-yl)acetate (**462G**):

Example 462G was prepared according to the method presented for the synthesis of Example 60E utilizing **462F** to provide the title compound: MS (m/z):364.1 [M+H]⁺.

20

Synthesis of ethyl 2-(4,4-difluoro-3-(trifluoromethyl)-4,4a,5,5a-tetrahydro-1H-cyclopropa[4,5]cyclopenta[1,2-c]pyrazol-1-yl)acetate (**462H**):

Example 462H was prepared according to the method presented for the synthesis of Example 60F utilizing **462G** to provide the title compound: MS (m/z):311.2 [M+H]⁺.

25

Synthesis of 2-(4,4-difluoro-3-(trifluoromethyl)-4,4a,5,5a-tetrahydro-1H-cyclopropa[4,5]cyclopenta[1,2-c]pyrazol-1-yl)acetic acid (**462I**):

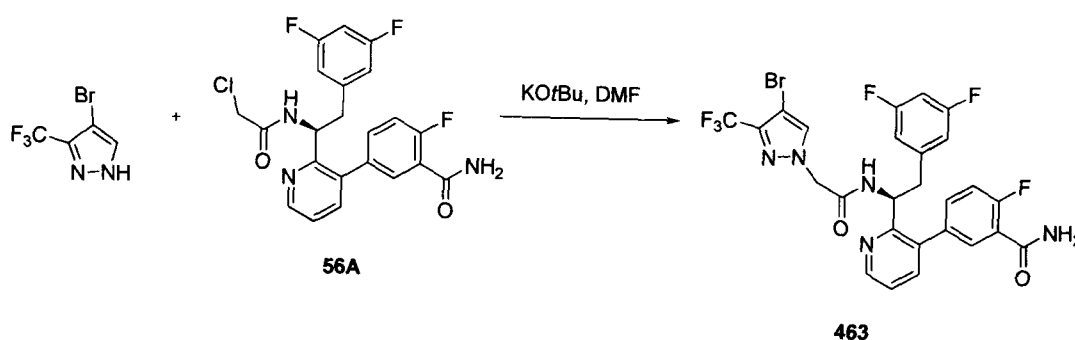
Example 462I was prepared according to the method presented for the synthesis of Example 60G utilizing **462H** to provide the title compound: MS (m/z):283.0 [M+H]⁺.

30

Synthesis of 5-(2-((1S)-1-(2-(4,4-difluoro-3-(trifluoromethyl)-4,4a,5,5a-tetrahydro-1H-cyclopropa[4,5]cyclopenta[1,2-c]pyrazol-1-yl)acetamido)-2-(3,5-difluorophenyl)ethyl)pyridin-3-yl)-2-fluorobenzamide (**462J**):

Example 462J was prepared (7.9 mg) according to the method presented for the synthesis of Example 13G utilizing **462I** and **54B** to provide the title compound: MS (m/z):636.4 [M+H]⁺. ¹H NMR of the mixture of diastereomers (400 MHz, cdcl₃) δ 10.07 (d, J = 7.2 Hz, 1H), 9.93 (d, J = 6.6 Hz, 1H), 8.78 (d, J = 5.4 Hz, 2H), 8.02 (d, J = 4.6 Hz, 2H), 7.74 (dd, J = 45.4, 39.5 Hz, 4H), 7.60 (m, 2H), 7.32 (t, J = 9.8 Hz, 2H), 6.94 (s, 2H), 6.80 – 6.60 (m, 4H), 6.15 (dd, J = 50.7, 43.2 Hz, 4H), 5.49 (dd, J = 15.6, 7.5 Hz, 2H), 4.95 – 4.72 (m, 4H), 3.31 – 3.13 (m, 2H), 3.13 – 2.94 (m, 2H), 2.63 (m, 2H), 2.36 (m, 2H), 1.37 (dd, J = 14.2, 7.3 Hz, 2H), 1.25 (s, 2H).

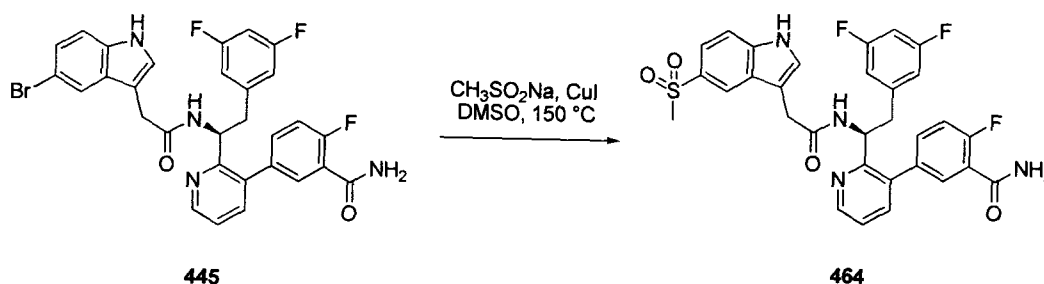
Example 463



Synthesis of (S)-5-(2-(1-(2-(4-bromo-3-(trifluoromethyl)-1H-pyrazol-1-yl)acetamido)-2-(3,5-difluorophenyl)ethyl)pyridin-3-yl)-2-fluorobenzamide (**463**):

Example 463 was prepared (5.2 mg) according to the method presented for the synthesis of Example 58D utilizing **56A** and 4-bromo-3-(trifluoromethyl)-1H-pyrazole to provide (S)-5-(2-(1-(2-(4-bromo-3-(trifluoromethyl)-1H-pyrazol-1-yl)acetamido)-2-(3,5-difluorophenyl)ethyl)pyridin-3-yl)-2-fluorobenzamide: MS (m/z): 626.6 [M+H]⁺; ¹H NMR (400 MHz, cdcl₃) δ 8.58 (d, J = 4.7 Hz, 1H), 7.61 (d, J = 10.6 Hz, 2H), 7.50 (d, J = 7.6 Hz, 1H), 7.41 (s, 1H), 7.39 – 7.13 (m, 3H), 6.77 (s, 1H), 6.55 (t, J = 8.7 Hz, 1H), 6.11 (d, J = 6.3 Hz, 2H), 5.84 (s, 1H), 5.43 (dd, J = 14.6, 7.9 Hz, 1H), 4.82 (s, 2H), 2.88 (dd, J = 16.9, 9.0 Hz, 2H).

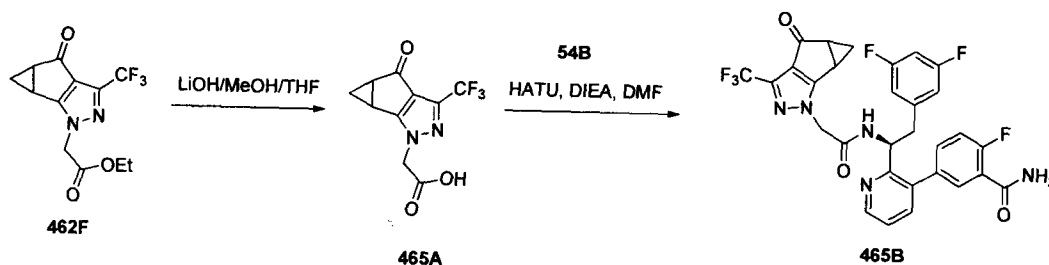
Example 464



Synthesis of (S)-5-(2-(2-(3,5-difluorophenyl)-1-(2-(5-(methylsulfonyl)-1H-indol-3-yl)acetamido)ethyl)pyridin-3-yl)-2-fluorobenzamide (**464**):

A solution of (S)-5-(2-(1-(2-(5-bromo-1H-indol-3-yl)acetamido)-2-(3,5-difluorophenyl)ethyl)pyridin-3-yl)-2-fluorobenzamide (30 mg, 0.04 mmol), CuI (33 mg, 0.17 mmol) and sodium methanesulfinate (17 mg, 0.17 mmol) in DMSO (1.5 mL) was subjected to microwave heating at 150 °C for 30 min. The reaction mixture was purified by reverse phase HPLC eluting with acetonitrile/water to afford 2.7 mg of the title compound.: MS (m/z): 607.3 [M+H]⁺; ¹H NMR (400 MHz, cdcl₃) δ 9.00 (s, 1H), 8.52 (s, 1H), 8.39 (d, J = 5.3 Hz, 1H), 8.04 – 7.89 (m, 2H), 7.65 (dd, J = 27.6, 8.5 Hz, 2H), 7.50 (d, J = 8.6 Hz, 1H), 7.38 – 7.23 (m, 1H), 6.92 (m, 1H), 6.58 (m, 1H), 6.28 (d, J = 5.9 Hz, 1H), 6.08 (s, 1H), 5.42 (d, J = 7.9 Hz, 1H), 3.81 (d, J = 15.7 Hz, 1H), 3.66 (d, J = 15.7 Hz, 1H), 3.22 – 3.05 (m, 1H), 3.02 (s, 3H), 2.99-2.96 (m, 1H).

Example 465



Synthesis of 2-(4-oxo-3-(trifluoromethyl)-4,4a,5,5a-tetrahydro-1H-cyclopropa[4,5]cyclopenta[1,2-c]pyrazol-1-yl)acetic acid (**465A**):

Example 465A was prepared according to the method presented for the synthesis of Example 60G utilizing **462F** to provide the title compound: MS (m/z):259.0 [M-H]⁻.

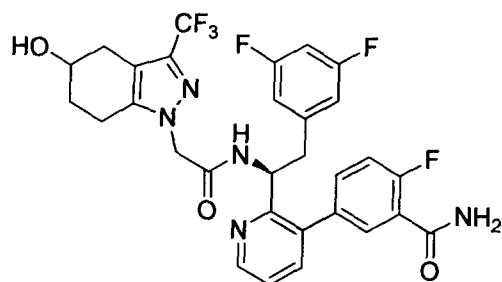
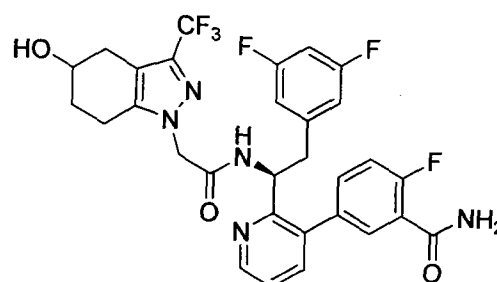
Synthesis of 5-(2-((1S)-2-(3,5-difluorophenyl)-1-(2-(4-oxo-3-(trifluoromethyl)-4,4a,5,5a-tetrahydro-1H-cyclopropa[4,5]cyclopenta[1,2-c]pyrazol-1-yl)acetamido)ethyl)pyridin-3-yl)-2-fluorobenzamide (**465B**):

Example 465B was prepared (18.7 mg) according to the method presented for the synthesis of Example 13G utilizing **465A** and **54B** to provide the title compound: MS (m/z):614.4 [M+H]⁺. ¹H NMR of the mixture of diastereomers (400 MHz, cdcl₃) δ 10.21 (d, J = 7.2 Hz, 1H), 10.06 (d, J = 7.0 Hz, 1H), 8.79 (d, J = 5.4 Hz, 2H), 8.11 – 8.00 (m, 2H), 7.90 – 7.77 (m, 4H), 7.63 (m, 2H), 7.32 (t, J = 9.9 Hz, 2H), 6.94 – 6.67 (m, 4H), 6.63 (t, J = 9.0 Hz, 2H), 6.24 (m, 4H), 5.51

(dd, $J = 14.8, 7.2$ Hz, 2H), 5.01 – 4.79 (m, 4H), 3.32 – 3.15 (m, 2H), 3.15 – 2.97 (m, 2H), 2.75 – 2.69 (m, 2H), 2.61 (d, $J = 4.4$ Hz, 2H), 1.85 – 1.57 (m, 4H).

Example 466 and 467

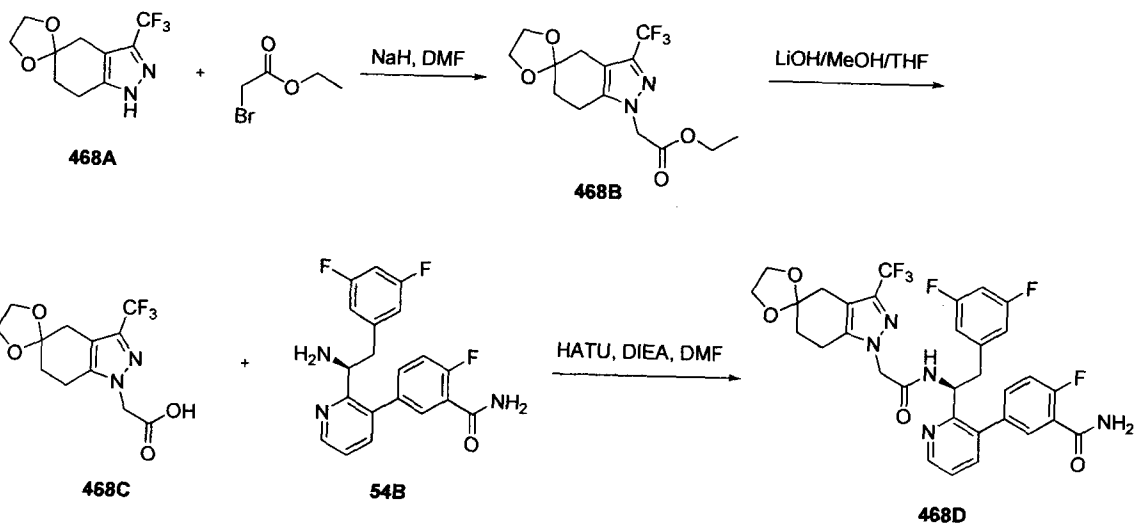
5

**466****467**

Synthesis of 5-(2-((1S)-2-(3,5-difluorophenyl)-1-(2-(5-hydroxy-3-(trifluoromethyl)-4,5,6,7-tetrahydro-1H-indazol-1-yl)acetamido)ethyl)pyridin-3-yl)-2-fluorobenzamide (**466**) and (**467**): Compound **448** was synthesized as a mixture of two diastereomers. Separation of **448** by chiral HPLC (Chiralpak IA, Heptane:Ethanol 80:20) provided **466** (5 mg, fast eluting peak, MS (m/z): 636.4 $[M+H]^+$) and **467** (7 mg, slow eluting peak, MS (m/z): 636.4 $[M+H]^+$).

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Example 468



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Synthesis of ethyl 2-(3'-(trifluoromethyl)-6',7'-dihydrospiro[[1,3]dioxolane-2,5'-indazole]-1'(4'H)-yl)acetate (**468B**):

To a solution of 3'-(trifluoromethyl)-1',4',6',7'-tetrahydrospiro[[1,3]dioxolane-2,5'-indazole] (5.0 g, 20 mmol) in DMF (100 mL) was added NaH (528 mg, 22 mmol) and ethyl 2-bromoacetate

(4.0 g, 24 mmol). The reaction was stirred at 80 °C for 2 h and was then poured into ethyl acetate and washed with saturated NH₄Cl solution and brine. The organic layer was dried over sodium sulfate, filtered and concentrated. MS (m/z): 335.2 [M+H]⁺; HPLC retention time 2.56 min (2-98% acetonitrile: water with 0.05% trifluoroacetic acid).

5

Synthesis of 2-(3'-(trifluoromethyl)-6',7'-dihydrospiro[[1,3]dioxolane-2,5'-indazole]-1'(4'H)-yl)acetic acid (**468C**):

The carboxylic acid **468C** was prepared according to the method presented for the synthesis of Example 60G utilizing ethyl 2-(3'-(trifluoromethyl)-6',7'-dihydrospiro[[1,3]dioxolane-2,5'-indazole]-1'(4'H)-yl)acetate to provide 2-(3'-(trifluoromethyl)-6',7'-dihydrospiro[[1,3]dioxolane-2,5'-indazole]-1'(4'H)-yl)acetic acid: MS (m/z): 306.8 [M+H]⁺; HPLC retention time 2.20 min (2-98% acetonitrile: water with 0.05% trifluoroacetic acid).

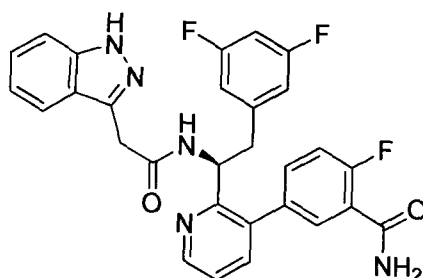
10

Synthesis of (S)-5-(2-(2-(3,5-difluorophenyl)-1-(2-(3'-(trifluoromethyl)-6',7'-dihydrospiro[[1,3]dioxolane-2,5'-indazole]-1'(4'H)-yl)acetamido)ethyl)pyridin-3-yl)-2-fluorobenzamide (**468D**):

Example **468D** was prepared (5.7 mg) according to the method presented for the synthesis of Example 13G utilizing **54B** and 2-(3'-(trifluoromethyl)-6',7'-dihydrospiro[[1,3]dioxolane-2,5'-indazole]-1'(4'H)-yl)acetic acid to provide the title compound: MS (m/z): 660.3 [M+H]⁺; HPLC retention time 1.06 min (2-98% acetonitrile: water with 0.05% trifluoroacetic acid). ¹H NMR (400 MHz, cd₃od) δ 8.68 (d, J = 3.0 Hz, 1H), 7.56 (dd, J = 7.8, 1.6 Hz, 1H), 7.46 – 7.33 (m, 2H), 7.28 (s, 1H), 7.23 (dd, J = 24.0, 13.5 Hz, 1H), 6.65 (d, J = 9.1 Hz, 1H), 6.33 (d, J = 6.3 Hz, 2H), 5.41 – 5.31 (m, 1H), 4.85 – 4.76 (m, 2H), 3.99 (s, 4H), 3.35 – 3.25 (m, 2H), 3.05 (dt, J = 19.7, 13.0 Hz, 2H), 2.82 – 2.68 (m, 2H), 2.63 (d, J = 6.8 Hz, 1H), 1.92 (dd, J = 14.2, 7.5 Hz, 3H).

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Example 469



469

Synthesis of 5-(2-(1-(2-(1H-indazol-3-yl)acetamido)-2-(3,5-difluorophenyl)ethyl)pyridin-3-yl)-2-fluorobenzamide (**469**):

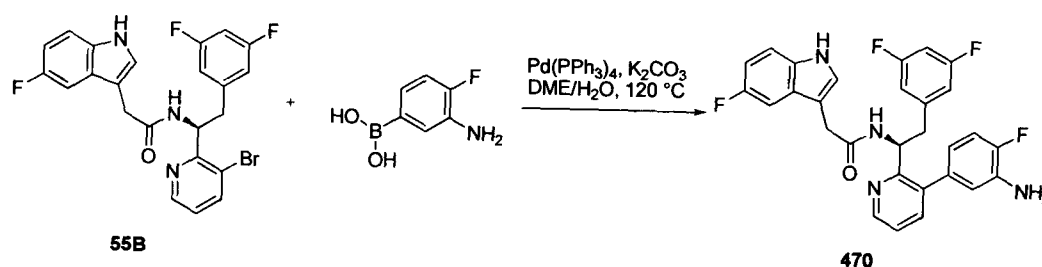
Example 469 was prepared (21.5 mg) according to the method presented for the synthesis of

5 Example 13G utilizing **54B** and 2-(1H-indazol-3-yl)acetic acid to provide the title compound:

MS (m/z): 530.5 [M+H]⁺; ¹H NMR (400 MHz, dmso) δ 8.91 (d, J = 8.0 Hz, 1H), 8.70 (d, J = 4.8 Hz, 1H), 7.62 (dd, J = 18.7, 9.7 Hz, 3H), 7.48 (d, J = 6.5 Hz, 1H), 7.45 – 7.35 (m, 4H), 7.25 (dd, J = 15.4, 8.1 Hz, 2H), 6.93 (dd, J = 14.6, 7.5 Hz, 2H), 6.57 (d, J = 6.7 Hz, 2H), 5.15 (t, J = 7.7 Hz, 1H), 3.78 – 3.64 (m, 2H), 3.02 (m, 2H).

10

Example 470

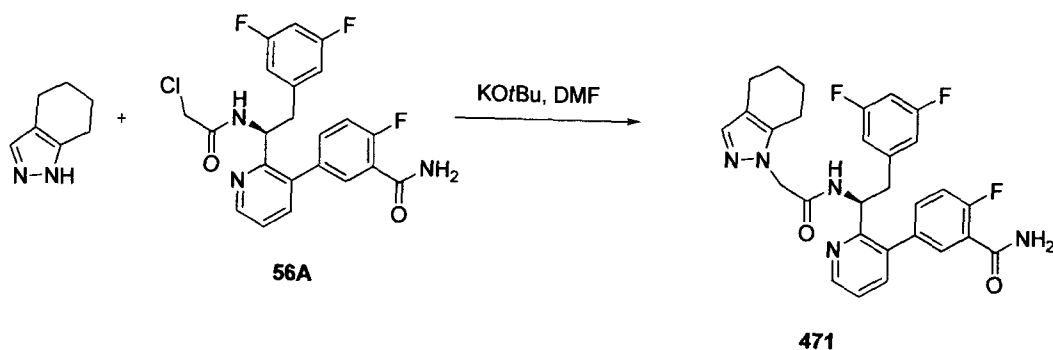


15 Synthesis of (S)-N-(1-(3-(3-amino-4-fluorophenyl)pyridin-2-yl)-2-(3,5-difluorophenyl)ethyl)-2-(5-fluoro-1H-indol-3-yl)acetamide (**470**):

To a solution of (S)-N-(1-(3-bromopyridin-2-yl)-2-(3,5-difluorophenyl)ethyl)-2-(5-fluoro-1H-indol-3-yl)acetamide (900 mg, 1.8 mmol) in a mixture of DME (6 mL) and H₂O (3 mL) was added 3-amino-4-fluorophenylboronic acid (370 mg, 2.4 mmol) and K₂CO₃ (552 mg, 4.0 mmol) and tetrakis triphenylphosphine palladium (115 mg, 0.1 mmol). The reaction tube was sealed and heated in a microwave reactor at 120 °C for 30 min. The reaction mixture was poured into ethyl acetate and washed with saturated NH₄Cl solution. The organic layer was dried over sodium sulfate, filtered and concentrated. The resulting residue was purified by silica gel chromatography eluting with EtOAc / hexanes to afford 630 mg of the title product. MS (m/z):

25 519.1 [M+H]⁺; HPLC retention time 3.85 min (2-98% acetonitrile: water with 0.05% trifluoroacetic acid). ¹H NMR (400 MHz, cdcl₃) δ 8.40 (s, 1H), 8.15 (s, 1H), 7.52 (s, 1H), 7.33 – 7.07 (m, 4H), 7.05 – 6.86 (m, 2H), 6.48 (dd, J = 36.6, 27.7 Hz, 3H), 6.37 (s, 1H), 6.12 (d, J = 7.2 Hz, 2H), 5.62 (q, J = 7.6 Hz, 1H), 3.81 (m, 1H), 3.67 (s, 2H), 2.86 (m, 1H).

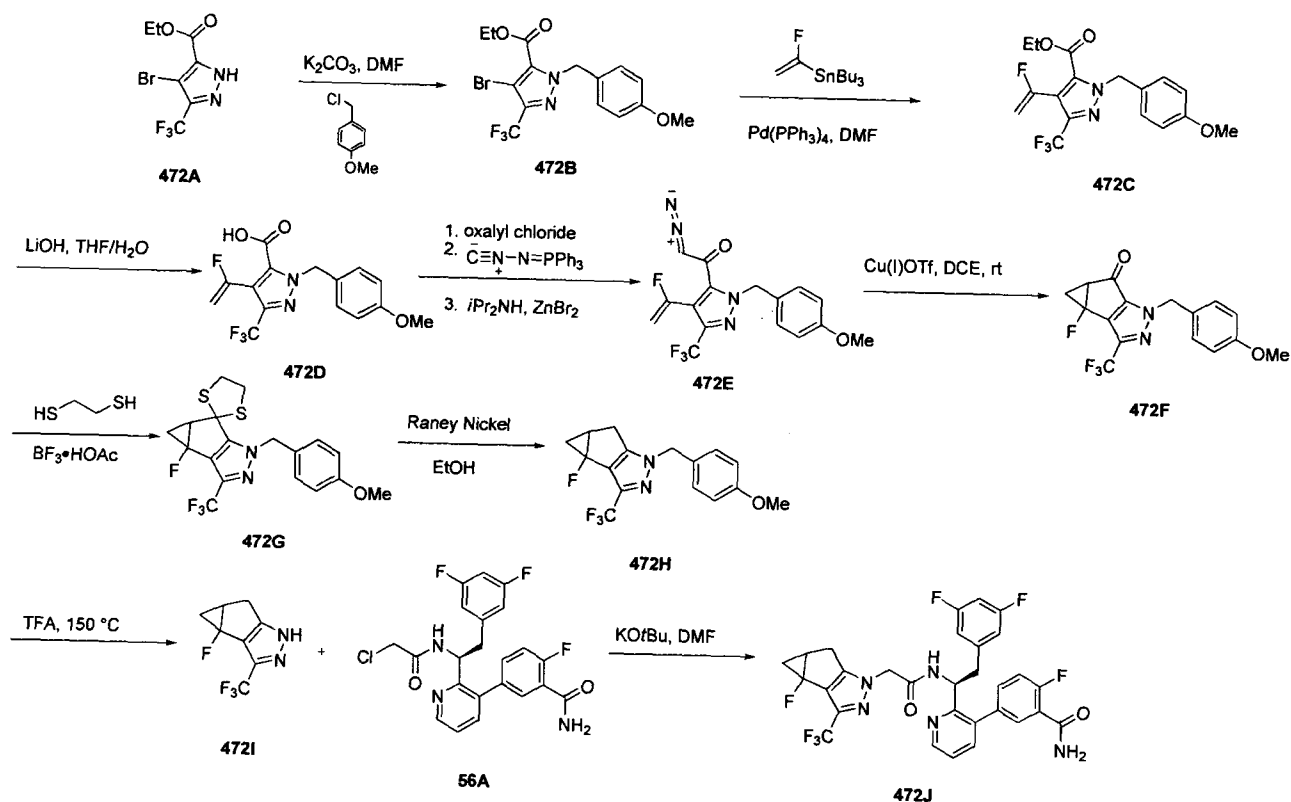
Example 471



Synthesis of (S)-5-(2-(2-(3,5-difluorophenyl)-1-(2-(4,5,6,7-tetrahydro-1H-indazol-1-yl)acetamido)ethyl)pyridin-3-yl)-2-fluorobenzamide (**471**):

- 5 Example 471 was prepared (21 mg) according to the method presented for the synthesis of Example 58D utilizing **56A** and 4,5,6,7-tetrahydro-1H-indazole to provide the title compound: MS (*m/z*): 534.0 [*M*+*H*]⁺; ¹H NMR (400 MHz, *cdCl*₃) 9.51 (s, 1H), 8.79 (d, *J* = 5.3 Hz, 1H), 7.94 (d, *J* = 7.8 Hz, 1H), 7.68 (dd, *J* = 28.6, 21.9 Hz, 1H), 7.59 – 7.53 (m, 1H), 7.53 – 7.19 (m, 2H), 6.97 (s, 1H), 6.61 (s, 1H), 6.22 (dd, *J* = 13.2, 6.5 Hz, 2H), 5.46 (d, *J* = 6.8 Hz, 1H), 4.98 (ddd, *J* = 41.3, 20.7, 13.7 Hz, 2H), 3.18 (dd, *J* = 12.9, 6.9 Hz, 1H), 3.11 – 2.95 (m, 1H), 2.71 (t, *J* = 6.2 Hz, 1H), 2.52 (d, *J* = 14.9 Hz, 3H), 1.83 (m, 2H), 1.77 (m, 2H).
- 10

Example 472



Synthesis of ethyl 4-bromo-1-(4-methoxybenzyl)-3-(trifluoromethyl)-1H-pyrazole-5-carboxylate (**472B**):

To a solution of ethyl 4-bromo-3-(trifluoromethyl)-1H-pyrazole-5-carboxylate (2.0 g, 7.0 mmol) in DMF (10 mL) was added K₂CO₃ (1.2 g, 8.4 mmol) and 1-(chloromethyl)-4-methoxybenzene (1.2 g, 7.7 mmol). The reaction was stirred at room temperature overnight and was then poured into ethyl acetate and washed with saturated NH₄Cl solution and brine. The organic layer was dried over sodium sulfate, filtered and concentrated. The resulting residue was purified by silica gel chromatography eluting with EtOAc / hexanes to afford 2.5 g of the title product. MS (m/z): 406.6 [M+H]⁺; HPLC retention time 1.60 min (2-98% acetonitrile: water with 0.05% trifluoroacetic acid).

Synthesis of ethyl 4-(1-fluorovinyl)-1-(4-methoxybenzyl)-3-(trifluoromethyl)-1H-pyrazole-5-carboxylate (**472C**):

To a solution of ethyl 4-bromo-1-(4-methoxybenzyl)-3-(trifluoromethyl)-1H-pyrazole-5-carboxylate (460 mg, 1.13 mmol) in DMF (6 mL) was added tributyl(1-fluorovinyl)stannane (492 mg, 1.4 mmol) and tetrakis triphenylphosphine palladium (130 mg, 0.12 mmol). The reaction was degassed with argon and heated at 100 °C overnight. The mixture was cooled to room temperature and then filtered through a pad of celite. The filtrate was diluted with ethyl acetate and washed with 5% LiCl solution and brine. The organic layer was dried over sodium sulfate, filtered and concentrated. The resulting residue was purified by silica gel chromatography eluting with EtOAc / hexanes to afford 400 mg of the title product. MS (m/z): 373.3 [M+H]⁺; HPLC retention time 1.61 min (2-98% acetonitrile: water with 0.05% trifluoroacetic acid).

Synthesis of 4-(1-fluorovinyl)-1-(4-methoxybenzyl)-3-(trifluoromethyl)-1H-pyrazole-5-carboxylic acid (**472D**):

The carboxylic acid **472D** was prepared according to the method presented for the synthesis of Example 60G utilizing ethyl 4-(1-fluorovinyl)-1-(4-methoxybenzyl)-3-(trifluoromethyl)-1H-pyrazole-5-carboxylate to provide 4-(1-fluorovinyl)-1-(4-methoxybenzyl)-3-(trifluoromethyl)-1H-pyrazole-5-carboxylic acid: MS (m/z): 342.8 [M-H]⁻; HPLC retention time 1.30 min (2-98% acetonitrile: water with 0.05% trifluoroacetic acid).

Synthesis of 2-diazo-1-(4-(1-fluorovinyl)-1-(4-methoxybenzyl)-3-(trifluoromethyl)-1H-pyrazol-5-yl)ethanone (**472E**):

To a solution of 4-(1-fluorovinyl)-1-(4-methoxybenzyl)-3-(trifluoromethyl)-1H-pyrazole-5-carboxylic acid (34 mg, 0.1 mmol) in dichloroethane (1 mL) was added DMF (0.01 mL) and oxalyl chloride (25 mg, 0.2 mmol). The reaction was stirred at room temperature for 30 min. After removing the volatiles in vacuo, the residue was dissolved in 1 mL dichloroethane. This solution was added to a suspension of isocyanoinminotriphenylphosphorane (45 mg, 0.15 mmol) in 1 mL dichloroethane. The reaction was stirred at room temperature for 1 h and water (0.5 mL) was added. The mixture was stirred overnight. The reaction was diluted with

dichloromethane and washed with brine. The organic layer was dried over sodium sulfate, filtered and concentrated. The resulting residue was purified by silica gel chromatography eluting with EtOAc / hexanes to afford 30 mg of (E)-2-(4-(1-fluorovinyl)-1-(4-methoxybenzyl)-3-(trifluoromethyl)-1H-pyrazol-5-yl)-2-oxoacetohydrazonoyl chloride: MS (m/z): 405.3 [M+H]⁺; HPLC retention time 1.40 min (2-98% acetonitrile: water with 0.05% trifluoroacetic acid). The product from the previous step was dissolved in 1 mL dichloroethane. To this solution was added diisopropylamine (10 mg, 0.096 mmol) and ZnBr₂ (3.3 mg, 0.015 mmol). The resulting solution was stirred at room temperature for 3 days. After removing the volatile in vacuo, the resulting residue was purified by reverse phase HPLC eluting with acetonitrile/water to afford 10 mg of the title compound.: MS (m/z): 369.0 [M+H]⁺.

Synthesis of 3b-fluoro-1-(4-methoxybenzyl)-3-(trifluoromethyl)-4,4a-dihydro-1H-cyclopropa[3,4]cyclopenta[1,2-c]pyrazol-5(3bH)-one (**472F**):

To a solution of 2-diazo-1-(4-(1-fluorovinyl)-1-(4-methoxybenzyl)-3-(trifluoromethyl)-1H-pyrazol-5-yl)ethanone (10 mg, 0.028 mmol) in dichloroethane (1 mL) was added Cu(OTf) (10 mg, 0.034 mmol). The reaction was stirred at room temperature for 3 h.. After removing the volatile in vacuo, the resulting residue was purified by reverse phase HPLC eluting with acetonitrile/water to afford 5 mg of the title compound.: MS (m/z): 341.0 [M+H]⁺.

Synthesis of 3b-fluoro-1-(4-methoxybenzyl)-3-(trifluoromethyl)-1,3b,4,4a-

tetrahydrospiro[cyclopropa[3,4]cyclopenta[1,2-c]pyrazole-5,2'-[1,3]dithiolane] (**472G**):

Example 472G was prepared according to the method presented for the synthesis of Example 60E utilizing **472F** to provide the title compound: MS (m/z): 417.1 [M+H]⁺.

Synthesis of 3b-fluoro-1-(4-methoxybenzyl)-3-(trifluoromethyl)-3b,4,4a,5-tetrahydro-1H-cyclopropa[3,4]cyclopenta[1,2-c]pyrazole (**472H**):

To a solution of **472G** (40 mg, 0.096 mmol) in ethanol (2 mL) was added Raney Nickel (1 mL slurry). The reaction was stirred at room temperature for 5 min. The insoluble solid were removed by filtration through a pad of celite. After removing the volatile in vacuo, the resulting residue was purified by reverse phase HPLC eluting with acetonitrile/water to afford the title compound: MS (m/z): 327.0 [M+H]⁺.

Synthesis of 3b-fluoro-3-(trifluoromethyl)-3b,4,4a,5-tetrahydro-1H-cyclopropa[3,4]cyclopenta[1,2-c]pyrazole (**472I**):

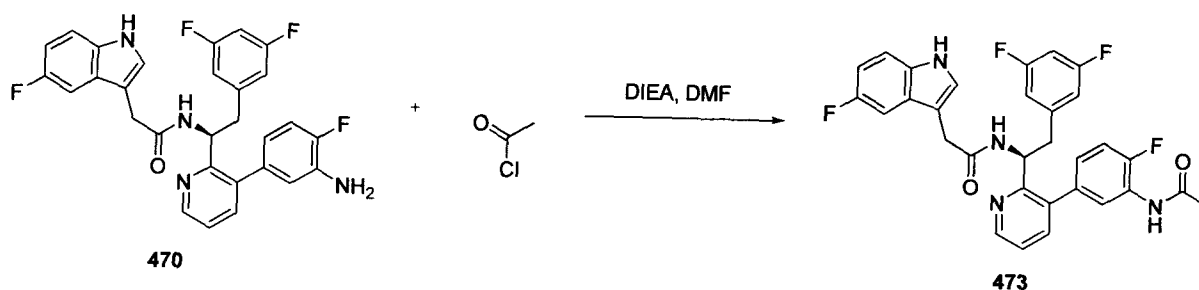
The solution of **472H** (20 mg, 0.06 mmol) in TFA (1 mL) was subjected to microwave heating at 150 °C for 10 min. After removing the volatile in vacuo, the resulting crude was used in the next step without further purification: MS (m/z): 207.1 [M+H]⁺.

Synthesis of 5-(2-((1S)-2-(3,5-difluorophenyl)-1-(2-(3b-fluoro-3-(trifluoromethyl)-3b,4,4a,5-tetrahydro-1H-cyclopropa[3,4]cyclopenta[1,2-c]pyrazol-1-yl)acetamido)ethyl)pyridin-3-yl)-2-fluorobenzamide (**472J**):

Example 472J was prepared (1.0 mg) according to the method presented for the synthesis of Example 13G utilizing **472I** and **54B** to provide the title compound: MS (m/z): 618.1 [M+H]⁺. ¹H

NMR of the mixture of diastereomers (400 MHz, cdcl₃) δ 9.45 (m, 1H), 9.30 (m, 1H), 8.74 (d, J = 4.1 Hz, 2H), 7.93 (s, 2H), 7.72 (s, 2H), 7.59 (s, 2H), 7.24 (m, 4H), 6.89 (s, 2H), 6.61 (s, 2H), 6.33 (s, 2H), 6.19 (s, 4H), 5.48 (s, 2H), 4.82 – 4.56 (m, 4H), 3.14 (m, 2H), 3.04 (m, 2H), 2.47 (m, 6H), 1.77 (m, 2H), 0.84 (m, 2H).

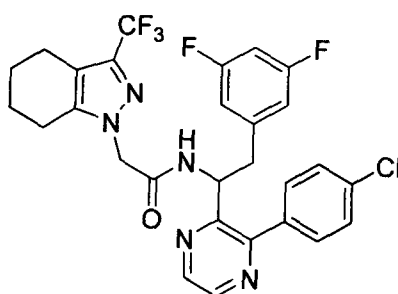
Example 473



Synthesis of (S)-N-(1-(3-(3-acetamido-4-fluorophenyl)pyridin-2-yl)-2-(3,5-difluorophenyl)ethyl)-2-(5-fluoro-1H-indol-3-yl)acetamide (**473**):

To a solution of (S)-N-(1-(3-(3-amino-4-fluorophenyl)pyridin-2-yl)-2-(3,5-difluorophenyl)ethyl)-2-(5-fluoro-1H-indol-3-yl)acetamide (10 mg, 0.02 mmol) in DMF (1 mL) was added acetyl chloride (2.4 mg, 0.03 mmol) and DIEA (3.9 mg, 0.03 mmol). The reaction was stirred at room temperature for 30 min. The reaction mixture was then purified by reverse phase HPLC eluting with acetonitrile/water to afford 6.7 mg of the title compound. MS (m/z): 561.0 [M+H]⁺; HPLC retention time 3.64 min (2-98% acetonitrile: water with 0.05% trifluoroacetic acid). ¹H NMR (400 MHz, cdcl₃) δ 8.58 (d, J = 5.3 Hz, 1H), 8.24 (d, J = 31.7 Hz, 2H), 8.14 (d, J = 7.7 Hz, 3H), 7.80 – 7.70 (m, 1H), 7.52 (s, 1H), 7.42 – 7.35 (m, 1H), 7.27 (d, J = 12.7 Hz, 1H), 6.88 (dd, J = 21.1, 9.4 Hz, 2H), 6.46 (s, 1H), 6.28 (d, J = 5.9 Hz, 2H), 5.49 – 5.41 (m, 1H), 3.63 (d, J = 2.7 Hz, 2H), 3.18 (d, J = 9.7 Hz, 1H), 3.07 (d, J = 6.8 Hz, 1H), 2.28 (s, 3H)

Example 474

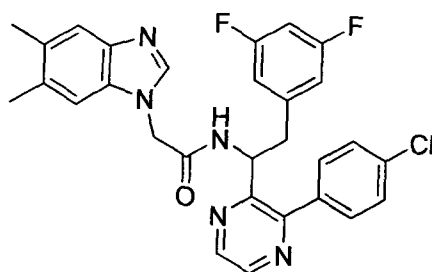


474

Synthesis of N-(1-(3-(4-chlorophenyl)pyrazin-2-yl)-2-(3,5-difluorophenyl)ethyl)-2-(3-(trifluoromethyl)-4,5,6,7-tetrahydro-1H-indazol-1-yl)acetamide (**474**):

Example 474 was prepared (10.7 mg) according to the method presented for the synthesis of Example 13G utilizing **443H** and 2-(3-(trifluoromethyl)-4,5,6,7-tetrahydro-1H-indazol-1-yl)acetic acid to provide the title product: MS (m/z): 576.2 [M+H]⁺; ¹H NMR (400 MHz, dmso) δ 9.10 (d, J = 8.1 Hz, 1H), 8.75 (s, 1H), 8.66 (s, 1H), 7.46 (dd, J = 24.0, 8.4 Hz, 4H), 6.98 (t, J = 9.4 Hz, 2H), 6.52 (d, J = 6.9 Hz, 2H), 5.31 (d, J = 7.2 Hz, 1H), 4.74 (s, 2H), 3.00 (dd, J = 36.7, 29.6 Hz, 2H), 2.46 (m, 4H), 2.33 (m, 1H), 2.27 (m, 1H), 1.63 (s, 4H).

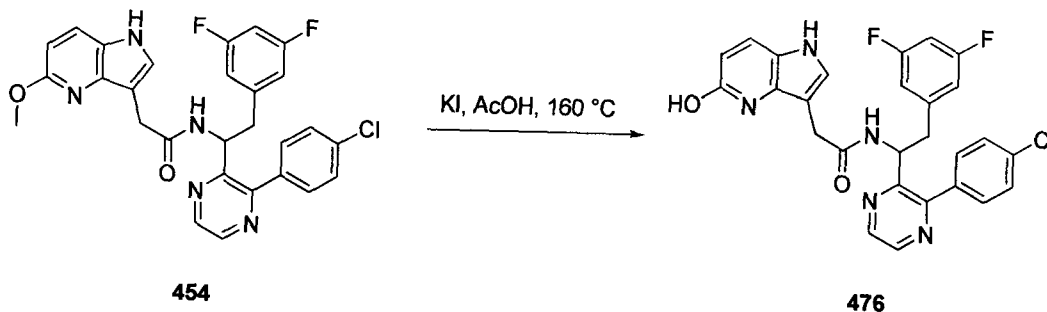
Example 475

**475**

Synthesis of N-(1-(3-(4-chlorophenyl)pyrazin-2-yl)-2-(3,5-difluorophenyl)ethyl)-2-(5,6-dimethyl-1H-benzo[d]imidazol-1-yl)acetamide (**475**):

- 5 Example 475 was prepared (8.3 mg) according to the method presented for the synthesis of Example 13G utilizing **443H** and 2-(5,6-dimethyl-1H-benzo[d]imidazol-1-yl)acetic acid to provide the title product: MS (m/z): 532.1 [M+H]⁺; ¹H NMR (400 MHz, dmsO) δ 9.42 (d, J = 8.0 Hz, 1H), 8.79 (s, 1H), 8.67 (s, 1H), 7.43 (dd, J = 21.2, 8.3 Hz, 4H), 7.22 (d, J = 6.5 Hz, 1H), 7.10 (s, 1H), 6.98 (s, 2H), 6.53 (d, J = 7.1 Hz, 2H), 5.31 (d, J = 7.6 Hz, 1H), 5.11 (s, 2H), 3.17 – 3.11 (m, 1H), 3.13 – 2.87 (m, 1H), 2.34 (s, 3H), 2.31 (s, 3H).

Example 476

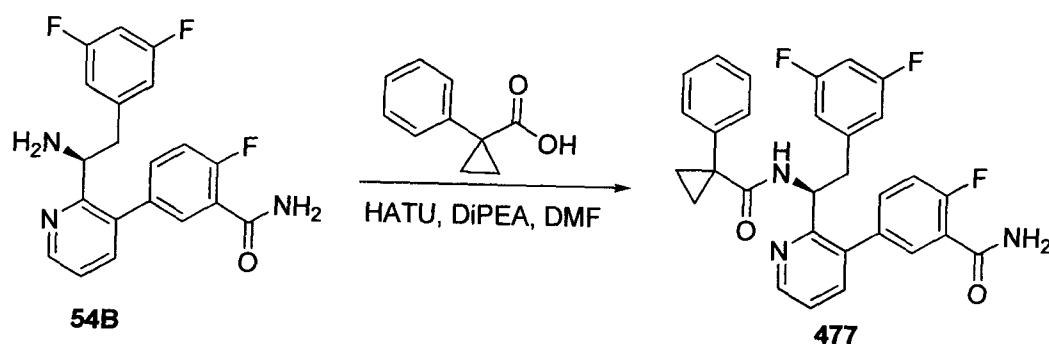
**476**

- 15 Synthesis of N-(1-(3-(4-chlorophenyl)pyrazin-2-yl)-2-(3,5-difluorophenyl)ethyl)-2-(5-hydroxy-1H-pyrrolo[3,2-b]pyridin-3-yl)acetamide (**476**):

A solution of N-(1-(3-(4-chlorophenyl)pyrazin-2-yl)-2-(3,5-difluorophenyl)ethyl)-2-(5-methoxy-1H-pyrrolo[3,2-b]pyridin-3-yl)acetamide (4.2 mg, 0.008 mmol) and KI (20 mg, 0.12 mmol) in 1 mL acetic acid in a sealed tube was subjected to microwave heating at 160 °C for 10 min. After removing the volatile in vacuo, the residue purified by reverse phase HPLC eluting with acetonitrile/water to afford 3.3 mg of the title compound. MS (m/z): 520.1 [M+H]⁺; ¹H NMR (400 MHz, dmsO) δ 11.38 (s, 1H), 8.82 – 8.70 (m, 2H), 8.63 (s, 1H), 7.79 (d, J = 8.9 Hz,

1H), 7.44 (d, J = 3.5 Hz, 4H), 7.13 (s, 1H), 6.90 (s, 1H), 6.42 (d, J = 6.0 Hz, 2H), 6.29 (d, J = 9.4 Hz, 1H), 5.29 (d, J = 7.6 Hz, 1H), 3.45 (d, J = 8.8 Hz, 2H), 3.21 – 2.91 (m, 2H).

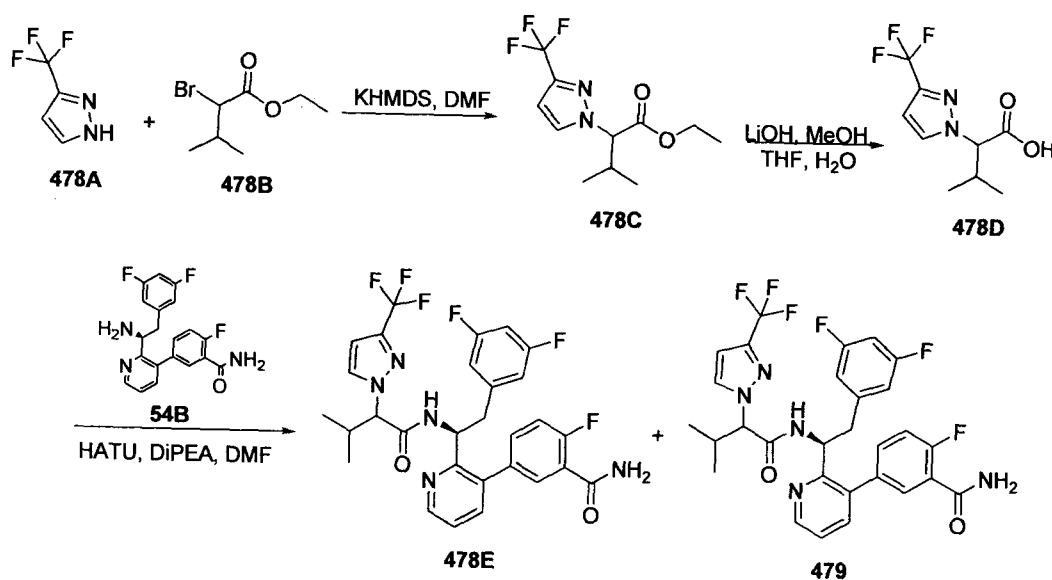
Example 477



Synthesis of (S)-5-(2-(2-(3,5-difluorophenyl)-1-(1-phenylcyclopropanecarboxamido)ethyl)pyridin-3-yl)-2-fluorobenzamide (**477**):

The title compound was prepared according to the method presented in the synthesis of **34E** substituting 1-phenylcyclopropanecarboxylic acid for **34D** and **54B** for (S)-2-(3,5-difluorophenyl)-1-(3-(4-methoxyphenyl)pyridin-2-yl)ethanamine to provide the desired compound (18.5 mg, 30%): ¹H NMR (400 MHz, dmsO) δ 8.45 (dd, 1H), 7.69 (d, 2H), 7.60 (dd, 1H), 7.54 – 7.48 (m, 1H), 7.42 (d, 1H), 7.34 (ddd, 5H), 7.23 (dd, 2H), 6.92 (t, 1H), 6.79 (d, 1H), 6.40 (d, 2H), 5.20 (dd, 1H), 2.80 (ddd, 2H), 1.17 (d, 2H), 0.91 (t, 2H); MS (*m/z*) 516.3 [M+H]⁺.

Examples 478 and 479



Synthesis of ethyl 3-methyl-2-(3-(trifluoromethyl)-1H-pyrazol-1-yl)butanoate (**478C**):

A 2 dram vial was charged with 3-(trifluoromethyl)-1H-pyrazole (500 mg, 3.8 mmol), DMF (5 ml), and KHMDS (1.1 g, 5.5 mmol). The resulting mixture was stirred for 10 minutes and then add ethyl 2-bromo-3-methylbutanoate (0.8 ml, 5.3 mmol). Stir at RT until done by LC/MS or TLC. Dilute the reaction with H₂O and extract 2X EtOAc. The combined organic layers were washed with brine then dried over sodium sulfate, concentrated, and purified by flash chromatography to give the desired compound (450 mg, 46%): MS (*m/z*) 265.2 [M+H]⁺.

Synthesis of 3-methyl-2-(3-(trifluoromethyl)-1H-pyrazol-1-yl)butanoic acid (**478D**):

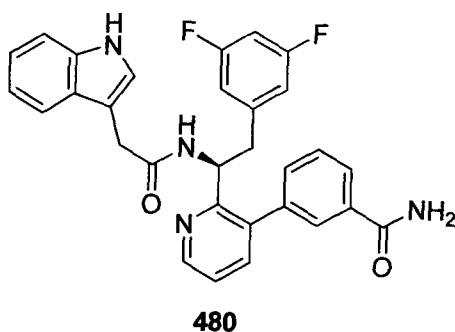
A 40 ml vial was charged with ethyl 3-methyl-2-(3-(trifluoromethyl)-1H-pyrazol-1-yl)butanoate (450 mg, 1.7 mmol), MeOH (2 ml), THF (5 ml), H₂O (2 ml), and LiOH (500 mg, 21 mmol). Stir at RT until done by LC/MS. Dilute the reaction with H₂O and extract with EtOAc. The water layer was acidified with 1 N HCl and extracted 2X EtOAc. The combined organic layers were dried over sodium sulfate, concentrated, and used crude in the next reaction: MS (*m/z*) 237.0 [M+H]⁺.

Synthesis of 5-(2-((1S)-2-(3,5-difluorophenyl)-1-(3-methyl-2-(3-(trifluoromethyl)-1H-pyrazol-1-yl)butanamido)ethyl)pyridin-3-yl)-2-fluorobenzamide (**478E** and **479**):

The title compounds were prepared according to the method presented in the synthesis of **54G** substituting 3-methyl-2-(3-(trifluoromethyl)-1H-pyrazol-1-yl)butanoic acid for 2-(5-

(trifluoromethyl)-1H-indol-3-yl)acetic acid to provide the desired compounds (**478E**, the first peak off HPLC 2.2 mg, 3%; **479**, the second peak off HPLC, 2.6 mg, 3%): **478E** ¹H NMR (400 MHz, dmso) δ 8.63 (d, 1H), 8.43 (d, 1H), 7.88 (s, 1H), 7.66 (s, 2H), 7.57 (d, 1H), 7.45 (d, 1H), 7.37 (dd, 1H), 7.31 (d, 2H), 6.90 (s, 1H), 6.56 (s, 1H), 6.50 (d, 2H), 5.11 (d, 1H), 2.90 (d, 2H), 2.72 – 2.60 (m, 2H), 1.44 (d, 6H). MS (*m/z*) 590.6 [M+H]⁺. **479** ¹H NMR (400 MHz, dmso) δ 9.21 (d, 1H), 8.60 (d, 1H), 7.85 (s, 1H), 7.70 (d, 2H), 7.60 (d, 1H), 7.53 (d, 1H), 7.45 – 7.28 (m, 3H), 6.94 (s, 1H), 6.64 (s, 3H), 5.16 (s, 1H), 4.69 (d, 1H), 2.99 (d, 3H), 0.50 (t, 6H); MS (*m/z*) 591.1 [M+H]⁺.

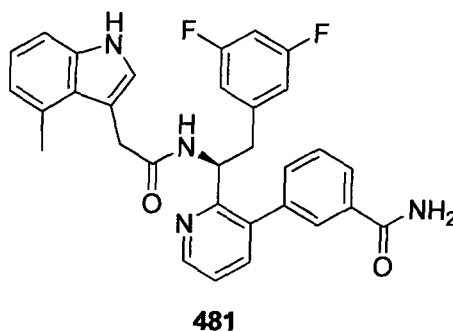
Example 480



Synthesis of (S)-3-(2-(1-(2-(1H-indol-3-yl)acetamido)-2-(3,5-difluorophenyl)ethyl)pyridin-3-yl)benzamide (**480**):

- 5 The title compound was prepared according to the method presented in the synthesis of **50D** utilizing **50C** and 2-(1H-indol-3-yl)acetic acid to provide 5.1 mg the desired compound in a 12% yield: ^1H NMR (400 MHz, dmso) δ 10.75 (s, 1H), 8.71 – 8.56 (m, 2H), 7.95 (s, 1H), 7.86 (d, 1H), 7.74 (s, 1H), 7.62 (dd, 1H), 7.50 – 7.35 (m, 4H), 7.26 (dd, 2H), 7.04 – 6.95 (m, 2H), 6.91 (t, 1H), 6.83 (t, 1H), 6.50 (d, 2H), 5.18 (dd, 1H), 3.45 (q, 2H), 2.95 (d, 2H); MS (m/z) 511.3
- 10 $[\text{M}+\text{H}]^+$.

Example 481



- 15 Synthesis of (S)-3-(2-(2-(3,5-difluorophenyl)-1-(2-(4-methyl-1H-indol-3-yl)acetamido)ethyl)pyridin-3-yl)benzamide (**481**):

The title compound was prepared according to the method presented in the synthesis of **50D** utilizing **50C** and 2-(4-methyl-1H-indol-3-yl)acetic acid to provide 17.6 mg of the desired compound in a 38% yield: ^1H NMR (400 MHz, dmso) δ 10.73 (s, 1H), 8.60 (dd, 1H), 8.28 (d, 1H), 7.95 (s, 1H), 7.88 (d, 1H), 7.74 (s, 1H), 7.61 (dd, 1H), 7.42 (ddd, 4H), 7.08 (d, 1H), 6.89 (ddd, 3H), 6.56 (d, 1H), 6.46 (d, 2H), 5.21 (dd, 2H), 3.68 – 3.53 (m, 2H), 2.93 (d, 2H), 2.28 (s, 3H); MS (m/z) 525.3 $[\text{M}+\text{H}]^+$.

20

482A

$\xrightarrow[\text{HATU, DMF, DiPEA}]{\text{H}_2\text{N}-\text{cyclopropyl}}$

482B

$\xrightarrow[\text{KHMDS, DMF}]{\text{56A}}$

482C

+

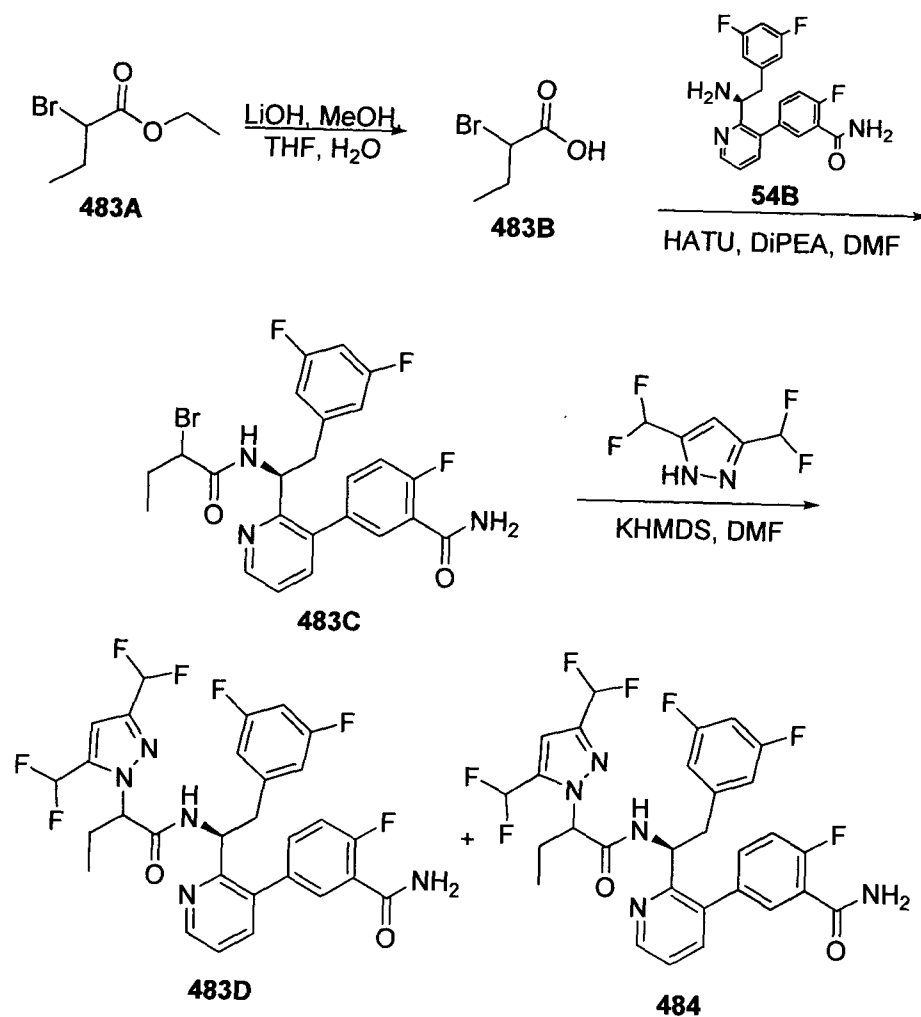
520

A RB was charged with 3-isopropyl-1H-pyrazole-5-carboxylic acid (500 mg, 3.2 mmol), DMF (10 ml), HATU (1.2 g, 3.2 mmol), cyclopropanamine (0.45 ml, 6.4 mmol), and DiPEA (2.2 ml, 13 mmol). Stir at RT until done by LC/MS or TLC. Dilute the reaction with H₂O and extract 2X EtOAc. The combined organic layers were concentrated, and used as is in the next reaction. MS (*m/z*) 193.0 [M+H]⁺.

Synthesis of (S)-1-(2-(1-(3-(3-carbamoyl-4-fluorophenyl)pyridin-2-yl)-2-(3,5-difluorophenyl)ethylamino)-2-oxoethyl)-N-cyclopropyl-5-isopropyl-1H-pyrazole-3-carboxamide (**482C**) and (S)-1-(2-(1-(3-(3-carbamoyl-4-fluorophenyl)pyridin-2-yl)-2-(3,5-difluorophenyl)ethylamino)-2-oxoethyl)-N-cyclopropyl-3-isopropyl-1H-pyrazole-5-carboxamide (**520**):

The title compounds were prepared according to the method presented in the synthesis of **56B** substituting N-cyclopropyl-3-isopropyl-1H-pyrazole-5-carboxamide for 1H-benzo[g]indole to provide the desired compounds (**482C** (as a 1:1 mix of **482C** and **520**), 3 mg, 7%; **520**, 8 mg, 20%): **482C** MS (*m/z*) 605.5 [M+H]⁺. **520** ¹H NMR (400 MHz, dmsO) δ 8.65 (d, 1H), 8.57 (d, 1H), 8.29 (d, 1H), 7.63 (s, 1H), 7.58 (d, 2H), 7.43 – 7.34 (m, 3H), 7.31 – 7.22 (m, 1H), 6.86 (s, 1H), 6.58 (s, 1H), 6.44 (d, 2H), 5.13 (d, 1H), 5.06 (s, 2H), 2.95 (d, 2H), 2.82 – 2.71 (m, 1H), 2.67 (s, 1H), 1.11 (d, 5H), 0.60 (d, 2H), 0.46 (s, 2H); MS (*m/z*) 605.4 [M+H]⁺.

Examples 483 and 484

Synthesis of 2-bromobutanoic acid (**483B**):

A 40 ml vial was charged with ethyl 2-bromobutanoate (0.7 ml, 5.1 mmol), MeOH (2 ml), THF (5 ml), H₂O (2 ml), and LiOH (1 g, 42 mmol). Stir at RT for 1 hour. Dilute the reaction with H₂O and extract with EtOAc. The water layer was acidified with 1 N HCl and extracted 2X EtOAc. The combined organic layers were dried over sodium sulfate, concentrated, and used crude in the next reaction.

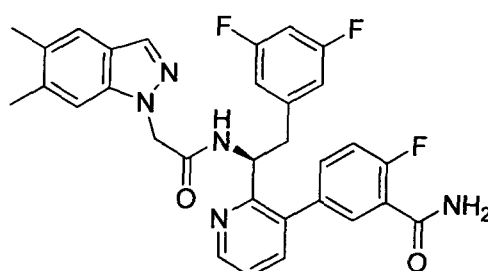
Synthesis of 5-(2-((1S)-1-(2-bromobutanamido)-2-(3,5-difluorophenyl)ethyl)pyridin-3-yl)-2-fluorobenzamide (**483C**):

The title compound was prepared according to the method presented in Example 54 substituting 2-bromobutanoic acid for 2-(5-(trifluoromethyl)-1H-indol-3-yl)acetic acid to provide the desired compound: MS (*m/z*) 522.0 [M+H]⁺.

Synthesis of 5-(2-((1S)-1-(2-(3,5-bis(difluoromethyl)-1H-pyrazol-1-yl)butanamido)-2-(3,5-difluorophenyl)ethyl)pyridin-3-yl)-2-fluorobenzamide (**483D** and **484**):

The title compounds were prepared according to the method presented in the synthesis of **56B** substituting 3,5-bis(difluoromethyl)-1H-pyrazole for 1H-benzo[g]indole and 5-(2-((1S)-1-(2-bromobutanamido)-2-(3,5-difluorophenyl)ethyl)pyridin-3-yl)-2-fluorobenzamide for **56A** to provide the desired compounds (**483D**, the first peak off HPLC, 3.7 mg, 6%; **484**, the second peak off HPLC, 21 mg, 36%): **483D** ¹H NMR (400 MHz, dmso) δ 8.81 (d, 1H), 8.62 (d, 1H), 7.65 (d, 1H), 7.59 (d, 1H), 7.48 (d, 1H), 7.38 (dd, 2H), 7.35 – 7.26 (m, 1H), 7.15 (s, 1H), 7.10 (s, 1H), 7.02 (s, 1H), 6.95 (d, 1H), 6.83 (s, 1H), 6.54 (d, 2H), 5.10 (d, 1H), 5.03 – 4.94 (m, 1H), 2.96 (d, 2H), 1.96 (s, 2H), 0.64 (t, 3H); MS (*m/z*) 608.8 [M+H]⁺. **484** ¹H NMR (400 MHz, dmso) δ 8.83 (d, 1H), 8.65 (d, 1H), 7.66 (s, 2H), 7.61 (d, 1H), 7.47 – 7.38 (m, 3H), 7.31 (dd, 1H), 7.12 (d, 1H), 6.98 (d, 1H), 6.90 – 6.80 (m, 2H), 6.49 (d, 2H), 5.08 (d, 1H), 5.03 – 4.93 (m, 1H), 2.96 (t, 2H), 2.10 – 1.90 (m, 2H), 0.68 (t, 3H); MS (*m/z*) 608.8 [M+H]⁺.

Example 485

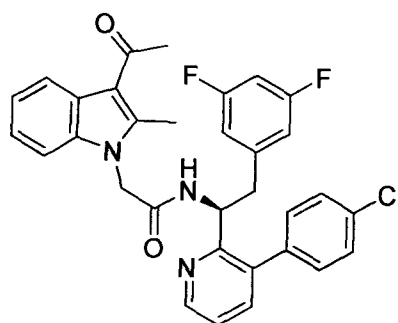


485

Synthesis of (S)-5-(2-(2-(3,5-difluorophenyl)-1-(2-(5,6-dimethyl-1H-indazol-1-yl)acetamido)ethyl)pyridin-3-yl)-2-fluorobenzamide (**485**):

The title compound was prepared according to the method presented in Example **56** substituting 5,6-dimethyl-1H-indazole for 1H-benzo[g]indole to provide the desired compound (13.6 mg, 38%): ¹H NMR (400 MHz, dmso) δ 8.82 (d, 1H), 8.71 – 8.65 (m, 1H), 7.80 (s, 1H), 7.66 – 7.55 (m, 3H), 7.41 (dd, 4H), 7.30 – 7.20 (m, 1H), 7.10 (s, 1H), 6.91 (t, 1H), 6.52 (d, 2H), 5.14 (dd, 1H), 4.95 (s, 2H), 2.99 (d, 2H), 2.25 (d, 6H); MS (*m/z*) 558.4 [M+H]⁺.

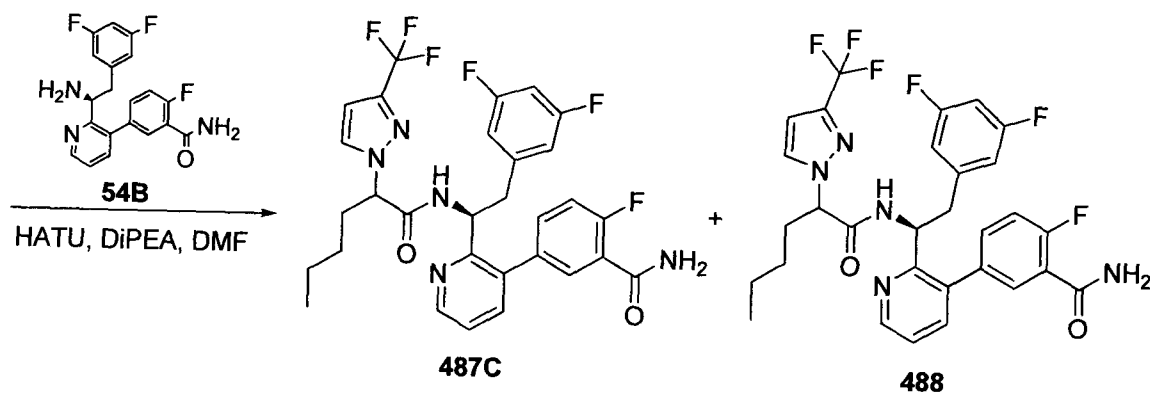
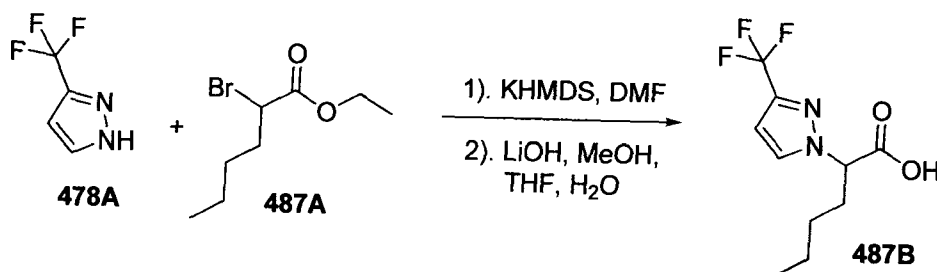
Example 486

**486**

Synthesis of (S)-2-(3-acetyl-2-methyl-1H-indol-1-yl)-N-(1-(3-(4-chlorophenyl)pyridin-2-yl)-2-(3,5-difluorophenyl)ethyl)acetamide (**486**):

The title compound was prepared according to the method presented in the synthesis of **36F** utilizing **36E** and 2-(3-acetyl-2-methyl-1H-indol-1-yl)acetic acid to provide 19.5 mg of the desired compound in a 29% yield: ^1H NMR (400 MHz, dmso) δ 9.12 (d, 1H), 8.69 (dd, 1H), 7.91 (d, 1H), 7.58 – 7.54 (m, 1H), 7.40 (dd, 3H), 7.24 (t, 3H), 7.15 – 7.05 (m, 2H), 6.98 (t, 1H), 6.50 (d, 2H), 5.15 (dd, 1H), 4.89 (d, 2H), 3.04 – 2.90 (m, 2H), 2.49 (s, 3H), 2.47 (s, 3H); MS (m/z) 558.5 $[\text{M}+\text{H}]^+$.

Examples 487 and 488



Synthesis of ethyl 2-(3-(trifluoromethyl)-1H-pyrazol-1-yl)hexanoate:

The title compound was prepared according to the method presented in Example **478**

substituting ethyl 2-bromohexanoate for ethyl 2-bromo-3-methylbutanoate to provide the desired compound: MS (m/z) 279.2 $[\text{M}+\text{H}]^+$.

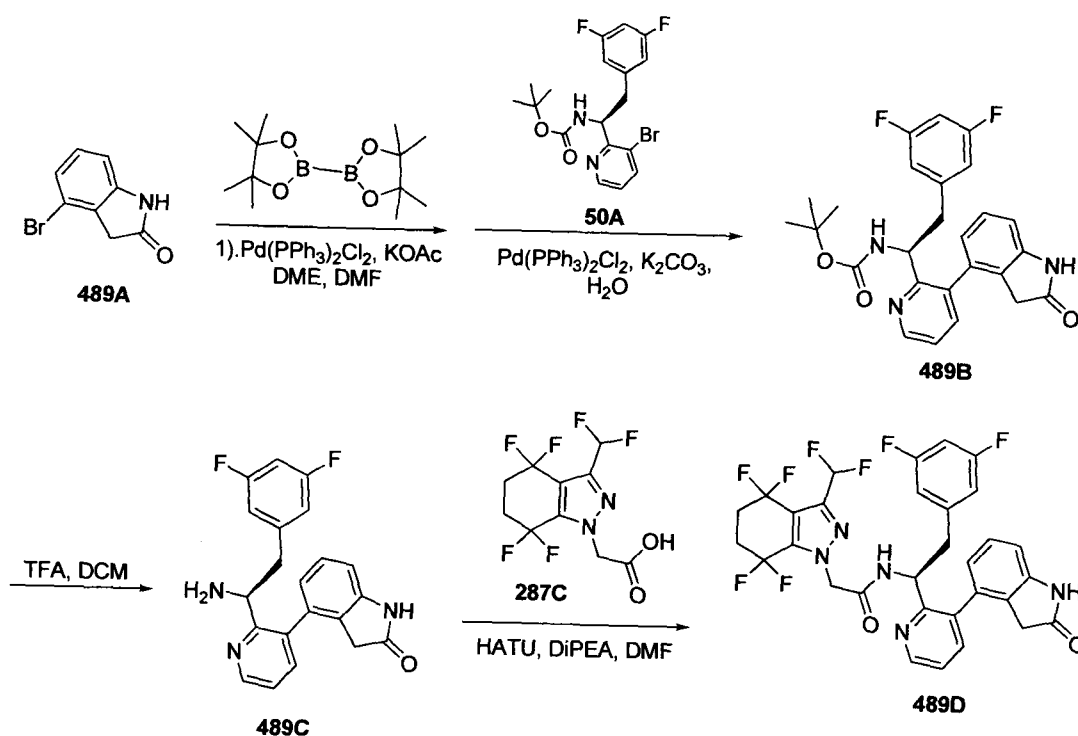
Synthesis of 2-(3-(trifluoromethyl)-1H-pyrazol-1-yl)hexanoic acid (**487B**):

The title compound was prepared according to the method presented in Example 478 substituting ethyl 2-(3-(trifluoromethyl)-1H-pyrazol-1-yl)hexanoate for ethyl 2-bromo-3-methylbutanoate to provide the desired compound: MS (m/z) 251.0 $[M+H]^+$.

Synthesis of 5-(2-((1S)-2-(3,5-difluorophenyl)-1-(2-(3-(trifluoromethyl)-1H-pyrazol-1-yl)hexanamido)ethyl)pyridin-3-yl)-2-fluorobenzamide (**487C** and **488**):

The title compounds were prepared according to the method presented in the synthesis of **54G** substituting 2-(3-(trifluoromethyl)-1H-pyrazol-1-yl)hexanoic acid for 2-(5-(trifluoromethyl)-1H-indol-3-yl)acetic acid to provide the desired compounds (**487C**, the first peak off HPLC, 6.5 mg, 8%; **488**, the second peak off HPLC, 6.1 mg, 8%): **487C** ^1H NMR (400 MHz, dmso) δ 9.11 (d, 1H), 8.65 – 8.59 (m, 1H), 7.84 (s, 1H), 7.69 (d, 2H), 7.62 (dd, 1H), 7.56 (d, 1H), 7.44 (s, 1H), 7.39 (dd, 1H), 7.35 – 7.27 (m, 1H), 6.97 (t, 1H), 6.68 (d, 2H), 6.63 (d, 1H), 5.12 (d, 1H), 5.00 (t, 1H), 3.00 (d, 2H), 1.78 – 1.67 (m, 2H), 1.15 (dd, 2H), 0.84 (s, 2H), 0.73 (t, 3H); MS (m/z) 605.0 $[M+H]^+$. **488** ^1H NMR (400 MHz, dmso) δ 9.02 (d, 1H), 8.65 (d, 1H), 7.87 (s, 1H), 7.67 – 7.57 (m, 3H), 7.47 – 7.36 (m, 3H), 7.35 – 7.27 (m, 1H), 6.83 (s, 1H), 6.63 (s, 1H), 6.45 (d, 2H), 5.14 – 4.97 (m, 2H), 2.98 (d, 2H), 1.85 (d, 2H), 1.17 (s, 2H), 0.98 (d, 2H), 0.73 (t, 3H); MS (m/z) 604.9 $[M+H]^+$.

Example 489



Synthesis of (S)-tert-butyl 2-(3,5-difluorophenyl)-1-(3-(2-oxoindolin-4-yl)pyridin-2-yl)ethylcarbamate (**489B**):

A microwave vial was charged with 4-bromoindolin-2-one (100 mg, 0.5 mmol), DME:DMF 4:1 (1.5 ml), 4,4,4',4',5,5,5',5'-octamethyl-2,2'-bi(1,3,2-dioxaborolane) (179mg, 0.8 mmol), $\text{Pd}(\text{PPh}_3)_2\text{Cl}_2$ (16 mg, 0.02 mmol), and KOAc (92 mg, 1 mmol). Heat the mixture in a microwave at 150 °C for 15 minutes. Then add **50A** (200 mg, 0.5 mmol), 2 M aq. K_2CO_3 (0.5 ml) and $\text{Pd}(\text{PPh}_3)_2\text{Cl}_2$ (16 mg, 0.02 mmol). Heat the mixture in a microwave at 150 °C for 20 minutes. Allow the reaction to cool then dilute with H_2O and extract 2X EtOAc. The combined organic layers were washed with brine then dried over sodium sulfate, concentrated, passed through a silica gel plug and concentrated to give the desired compound, which was used as is in the next reaction: MS (m/z) 466.3 $[\text{M}+\text{H}]^+$.

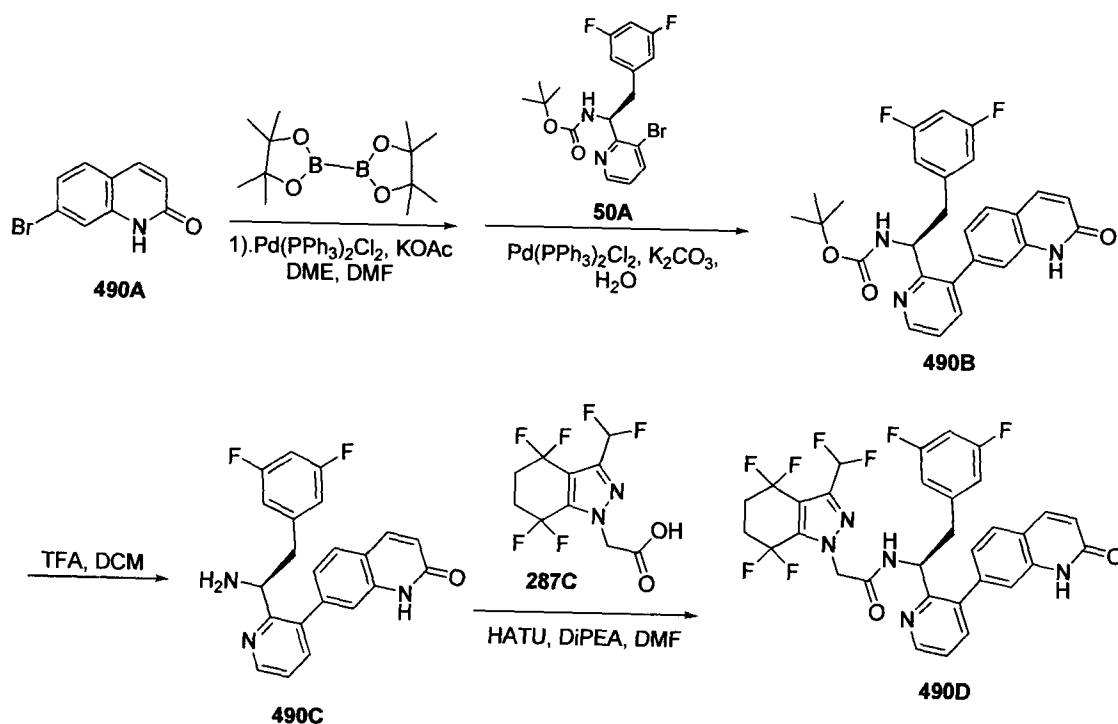
Synthesis of (S)-4-(2-(1-amino-2-(3,5-difluorophenyl)ethyl)pyridin-3-yl)indolin-2-one(**489C**):

The title compound was prepared according to the method presented in the synthesis of **50C** substituting (S)-tert-butyl 2-(3,5-difluorophenyl)-1-(3-(2-oxoindolin-4-yl)pyridin-2-yl)ethylcarbamate for **50B** to provide the desired compound: MS (m/z) 366.4 $[\text{M}+\text{H}]^+$.

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-(3-(2-oxoindolin-4-yl)pyridin-2-yl)ethyl)acetamide (**489D**):

The title compound was prepared according to the method presented in the synthesis of **61F** substituting **287C** for **61C** and **489C** for **61E** to provide the desired compound (17 mg): ^1H NMR (400 MHz, cd_3od) δ 8.70 (d, 1H), 7.66 (s, 1H), 7.57 (s, 1H), 7.40 (s, 1H), 7.26 (s, 1H), 7.18 (s, 1H), 6.97 (s, 1H), 6.90 (d, 1H), 6.78 (s, 1H), 6.71 (s, 2H), 6.37 (s, 1H), 6.29 (s, 1H), 6.23 (s, 1H), 5.05 (d, 3H), 3.17 – 3.04 (m, 2H), 2.98 (dd, 1H), 2.51 (s, 4H); MS (m/z) 650.2 $[\text{M}+\text{H}]^+$.

Example 490



Synthesis of (S)-tert-butyl 2-(3,5-difluorophenyl)-1-(3-(2-oxo-1,2-dihydroquinolin-7-yl)pyridin-2-yl)ethylcarbamate (**490B**):

The title compound was prepared according to the method presented in the synthesis of **489B** substituting 7-bromoquinolin-2(1H)-one for **489A** to provide the desired compound: MS (m/z) 478.1 $[\text{M}+\text{H}]^+$.

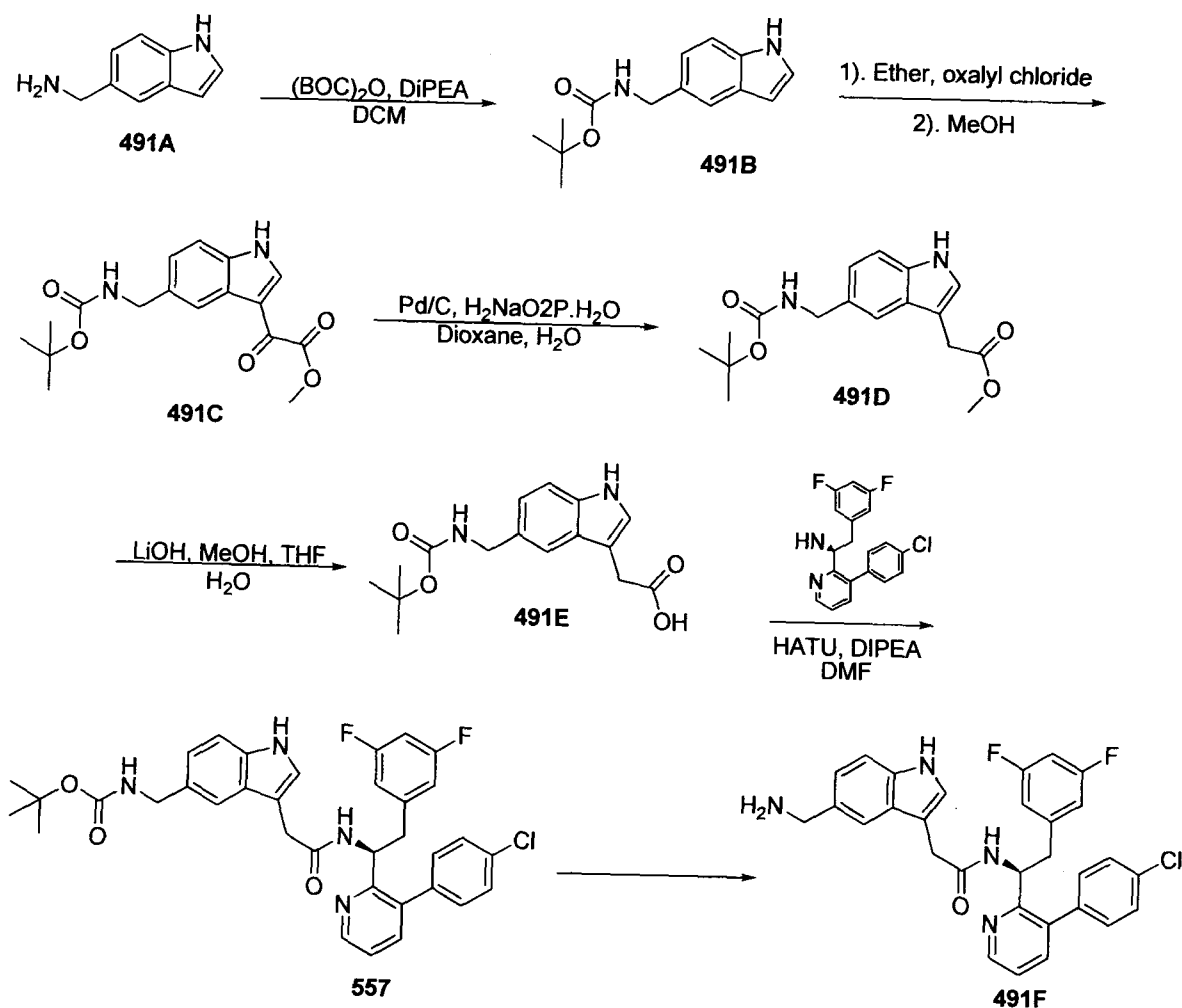
Synthesis of (S)-7-(2-(1-amino-2-(3,5-difluorophenyl)ethyl)pyridin-3-yl)quinolin-2(1H)-one (**490C**):

The title compound was prepared according to the method presented in the synthesis of **50C** substituting (S)-tert-butyl 2-(3,5-difluorophenyl)-1-(3-(2-oxo-1,2-dihydroquinolin-7-yl)pyridin-2-yl)ethylcarbamate for **50B** to provide the desired compound: MS (m/z) 378.1 $[\text{M}+\text{H}]^+$.

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-(3-(2-oxo-1,2-dihydroquinolin-7-yl)pyridin-2-yl)ethyl)acetamide (**490D**):

The title compound was prepared according to the method presented in the synthesis of **61F** substituting **287C** for **61C** and **490C** for **61E** to provide the desired compound (17 mg): ^1H NMR (400 MHz, cd_3od) δ 8.74 – 8.66 (m, 1H), 7.97 (d, 1H), 7.67 – 7.56 (m, 2H), 7.41 (dd, 1H), 7.06 (s, 1H), 6.94 (s, 1H), 6.81 (s, 1H), 6.65 (dd, 2H), 6.20 (d, 2H), 5.49 (t, 1H), 5.10 (s, 2H), 3.00 (d, 2H), 2.62 – 2.42 (m, 4H); MS (m/z) 662.3 $[\text{M}+\text{H}]^+$.

Examples 491 and 557



Synthesis of tert-butyl (1H-indol-5-yl)methylcarbamate (**491B**):

A round bottom flask was charged with (1H-indol-5-yl)methanamine (2 g, 14 mmol), $(\text{BOC})_2\text{O}$ (3 g, 14 mmol), DCM (100 ml), and DiPEA (2.4 ml, 14 mmol). The reaction was stirred until done by LC/MS. The reaction was diluted with H_2O and extracted 2X DCM and 1X EtOAc. The

combined organic layer was dried over sodium sulfate, filtered, concentrated and used crude in the next reaction. MS (m/z) 246.9 $[M+H]^+$

Synthesis of methyl 2-(5-((tert-butoxycarbonylamino)methyl)-1H-indol-3-yl)-2-oxoacetate (491C):

A round bottom flask was charged with ether (20 ml) and tert-butyl (1H-indol-5-yl)methylcarbamate (3g, 12 mmol) followed by slow addition of oxalyl chloride (1 ml, 11 mmol). The reaction was stirred until color changes and was then filtered. The solid was dissolved in MeOH (5 ml) and then precipitated out by adding ether. The mixture was filtered and dried under vacuum to obtain 1.4 g of the desired compound as the HCl salt which was used with no further purification. The yield was 36%.

Synthesis of methyl 2-(5-((tert-butoxycarbonylamino)methyl)-1H-indol-3-yl)acetate (491D):

A round bottom is charged with methyl 2-(5-((tert-butoxycarbonylamino)methyl)-1H-indol-3-yl)-2-oxoacetate (1.4 g, 4 mmol), dioxane (100 ml), Pd/C (0.5 g), $H_2NaO_2P \cdot H_2O$ (1 g, 9 mmol), and H_2O (40 ml). The resulting mixture was stirred at 120 °C until done as indicated by LC/MS. The reaction mixture was cooled to RT and filtered over a plug of celite, rinsing with ethyl acetate. The layers were partitioned and the organic layer was dried over sodium sulfate, filtered, concentrated and purified by flash chromatography to give the desired compound as an oil (660 mg, 52%): MS (m/z) 318.8 $[M+H]^+$

Synthesis of 2-(5-((tert-butoxycarbonylamino)methyl)-1H-indol-3-yl)acetic acid (491E):

The title compound was prepared according to the method presented in Example 478 substituting ethyl 2-(3-(trifluoromethyl)-1H-pyrazol-1-yl)hexanoate for methyl 2-(5-((tert-butoxycarbonylamino)methyl)-1H-indol-3-yl)acetate to provide the desired compound: MS (m/z) 305.1 $[M+H]^+$.

Synthesis of (S)-tert-butyl (3-(2-(1-(3-(4-chlorophenyl)pyridin-2-yl)-2-(3,5-difluorophenyl)ethylamino)-2-oxoethyl)-1H-indol-5-yl)methylcarbamate (557):

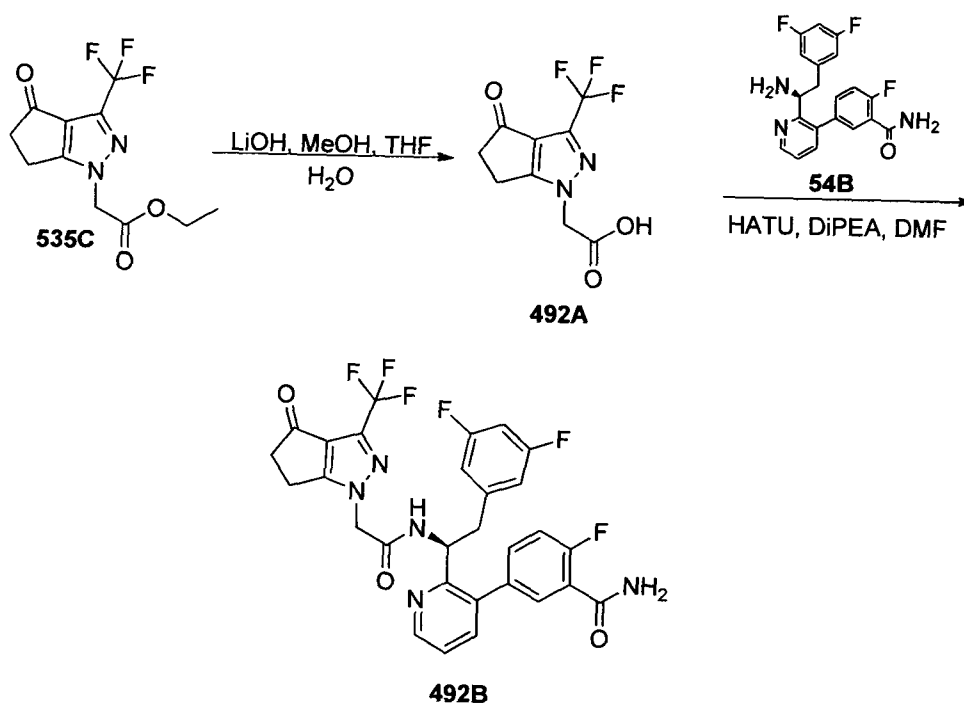
The title compound was prepared according to the method presented in the synthesis of 36F utilizing 36E and 2-(5-((tert-butoxycarbonylamino)methyl)-1H-indol-3-yl)acetic acid to provide 20 mg of the desired compound in a 29% yield: 1H NMR (400 MHz, dmsO) δ 10.72 (s, 1H), 8.63 (d, 1H), 8.50 (d, 1H), 7.51 (d, 1H), 7.36 (dd, 3H), 7.28 – 7.11 (m, 5H), 7.01 (s, 1H), 6.97 – 6.87

(m, 2H), 6.37 (d, 2H), 5.15 (d, 1H), 4.09 (s, 2H), 3.46 (s, 2H), 2.93 (s, 2H), 1.34 (s, 9H); MS (m/z) 631.5 $[M+H]^+$.

Synthesis of (S)-2-(5-(aminomethyl)-1H-indol-3-yl)-N-(1-(3-(4-chlorophenyl)pyridin-2-yl)-2-(3,5-difluorophenyl)ethyl)acetamide (**491F**):

A round bottom flask was charged (S)-tert-butyl (3-(2-(1-(3-(4-chlorophenyl)pyridin-2-yl)-2-(3,5-difluorophenyl)ethylamino)-2-oxoethyl)-1H-indol-5-yl)methylcarbamate (18 mg, 0.3 mmol) and TFA:DCM 1:1 (1 ml). The reaction was stirred at room temperature until done by LC/MS then concentrated 2X from DCM and then dissolved in ACN/H₂O and dried by lyophilization to obtain the desired compound (15 mg, 99%): ¹H NMR (400 MHz, dmso) δ 10.94 (s, 1H), 8.64 (dd, 1H), 8.54 (d, 1H), 8.00 (s, 2H), 7.54 (dd, 1H), 7.47 (s, 1H), 7.42 – 7.30 (m, 4H), 7.19 (d, 2H), 7.11 (d, 2H), 6.91 (t, 1H), 6.40 (d, 2H), 5.14 (dd, 1H), 3.99 (d, 2H), 3.48 (dd, 2H), 2.99 – 2.87 (m, 2H); MS (m/z) 531.4 $[M+H]^+$.

Example 492



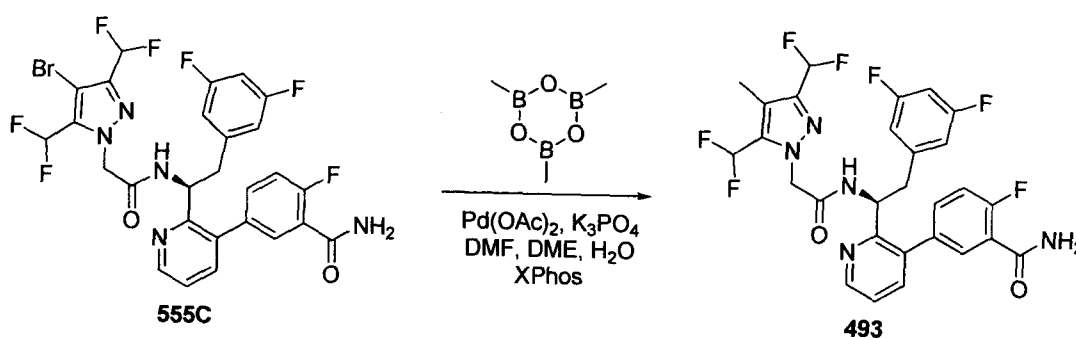
Synthesis of 2-(4-oxo-3-(trifluoromethyl)-5,6-dihydrocyclopenta[c]pyrazol-1(4H)-yl)acetic acid (**492A**):

The title compound was prepared according to the method presented in Example 491 substituting ethyl 2-(4-oxo-3-(trifluoromethyl)-5,6-dihydrocyclopenta[c]pyrazol-1(4H)-yl)acetate for **491D** to provide the desired compound: MS (m/z) 249.0 $[M+H]^+$.

Synthesis of (S)-5-(2-(2-(3,5-difluorophenyl)-1-(2-(4-oxo-3-(trifluoromethyl)-5,6-dihydrocyclopenta[c]pyrazol-1(4H)-yl)acetamido)ethyl)pyridin-3-yl)-2-fluorobenzamide (**492B**):

The title compound was prepared according to the method presented in the synthesis of **54G** utilizing **54B** and 2-(4-oxo-3-(trifluoromethyl)-5,6-dihydrocyclopenta[c]pyrazol-1(4H)-yl)acetic acid to provide 15.3 mg of the desired compound in a 19 % yield: ^1H NMR (400 MHz, cd_3od) δ 8.70 (d, 1H), 7.63 – 7.57 (m, 1H), 7.48 (s, 1H), 7.41 (dd, 1H), 7.30 (s, 1H), 7.25 – 7.16 (m, 1H), 6.67 (d, 1H), 6.33 (d, 2H), 5.36 (t, 1H), 4.95 (s, 2H), 3.33 (s, 2H), 3.08 (dd, 4H), 2.96 (d, 2H); MS (m/z) 602.5 $[\text{M}+\text{H}]^+$.

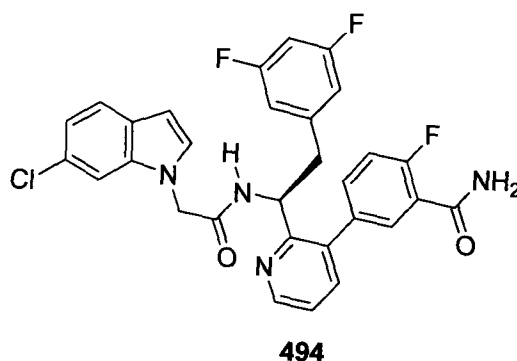
Example 493



Synthesis of (S)-5-(2-(1-(2-(3,5-bis(di-fluoromethyl)-4-methyl-1H-pyrazol-1-yl)acetamido)-2-(3,5-difluorophenyl)ethyl)pyridin-3-yl)-2-fluorobenzamide (**493**):

A 40 ml vial was charged with **555C** (100 mg, 0.15 mmol), DMF (1 ml), DME (4 ml), 2,4,6-trimethyl-1,3,5,2,4,6-trioxatriborinane (0.1 ml), $\text{Pd}(\text{OAc})_2$ (10 mg, 0.01 mmol), XPhos (14 mg, 0.02 mmol) and 2N K_3PO_4 (0.6 ml). Heat the stirring mixture overnight at 86 °C. Allow the reaction to cool then dilute with H_2O and extract 2X EtOAc. The combined organic layers were washed with brine then dried over sodium sulfate, concentrated, and purified by HPLC to give 8 mg of the desired compound. The yield was 9 %: ^1H NMR (400 MHz, cd_3od) δ 8.73 – 8.67 (m, 1H), 7.65 – 7.56 (m, 1H), 7.49 – 7.37 (m, 2H), 7.29 (s, 1H), 7.26 – 7.16 (m, 1H), 7.09 – 6.68 (m, 2H), 6.65 (t, 1H), 6.30 (d, 2H), 5.36 – 5.28 (m, 1H), 4.97 (s, 2H), 3.12 – 2.96 (m, 2H), 2.21 (s, 3H); MS (m/z) 594.3 $[\text{M}+\text{H}]^+$.

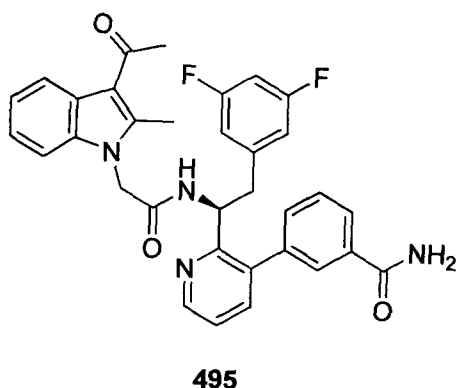
Example 494



Synthesis of (S)-5-(2-(1-(2-(6-chloro-1H-indol-1-yl)acetamido)-2-(3,5-difluorophenyl)ethyl)pyridin-3-yl)-2-fluorobenzamide (**494**):

The title compound was prepared according to the method presented in Example 56 substituting 6-chloro-1H-indole for 1H-benzo[g]indole to provide the desired compound (3 mg, 8%): ¹H NMR (400 MHz, dmso) δ 8.98 (d, 1H), 8.71 (s, 1H), 7.64 (s, 2H), 7.58 (d, 1H), 7.46 (d, 2H), 7.40 (d, 2H), 7.27 (d, 1H), 7.22 (s, 1H), 7.18 (d, 1H), 6.95 (d, 1H), 6.90 (s, 1H), 6.55 (d, 2H), 6.36 (d, 1H), 5.13 (d, 1H), 4.78 (s, 2H), 3.00 (d, 2H); MS (*m/z*) 563.8 [M+H]⁺.

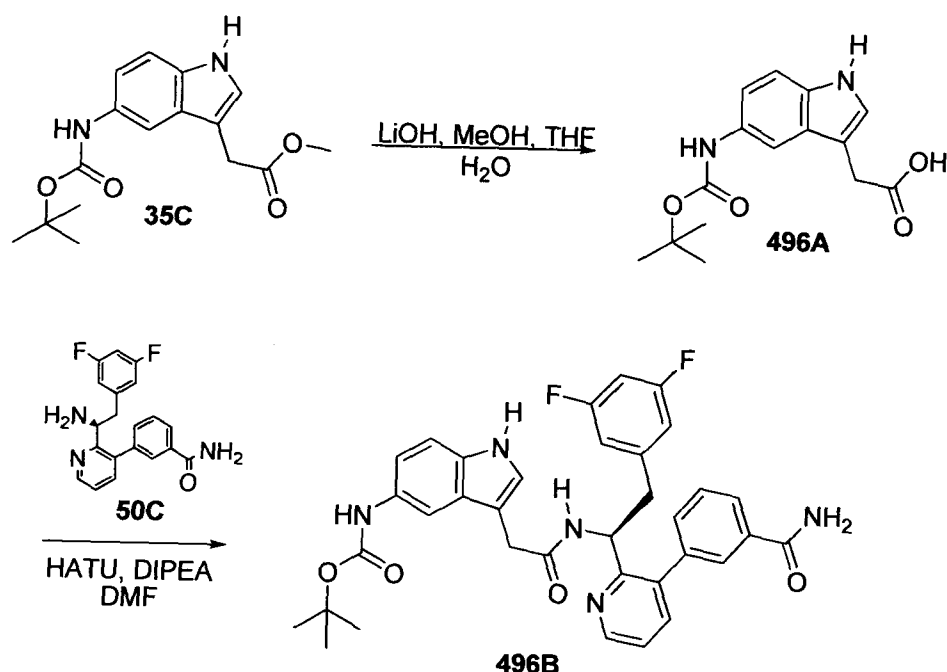
10 Example 495



Synthesis of (S)-3-(2-(1-(2-(3-acetyl-2-methyl-1H-indol-1-yl)acetamido)-2-(3,5-difluorophenyl)ethyl)pyridin-3-yl)benzamide (**495**):

The title compound was prepared according to the method presented in the synthesis of **50D** utilizing **50C** and 2-(3-acetyl-2-methyl-1H-indol-1-yl)acetic acid to provide 20 mg of the desired compound in a 32% yield: ¹H NMR (400 MHz, dmso) δ 9.10 (d, 1H), 8.75 – 8.65 (m, 1H), 7.90 (dd, 3H), 7.75 (s, 1H), 7.65 (dd, 1H), 7.49 – 7.35 (m, 4H), 7.22 (d, 1H), 7.15 – 7.02 (m, 2H), 6.94 (t, 1H), 6.58 (d, 2H), 5.17 (d, 1H), 4.86 (d, 2H), 3.01 (d, 2H), 2.48 (s, 3H), 2.46 (s, 2H); MS (*m/z*) 567.4 [M+H]⁺.

Example 496



Synthesis of 2-(5-(tert-butoxycarbonylamino)-1H-indol-3-yl)acetic acid (**496A**):

The title compound was prepared according to the method presented in Example **54** substituting **35C** for **54E** to provide the desired compound: MS (m/z) 291.1 $[M+H]^+$.

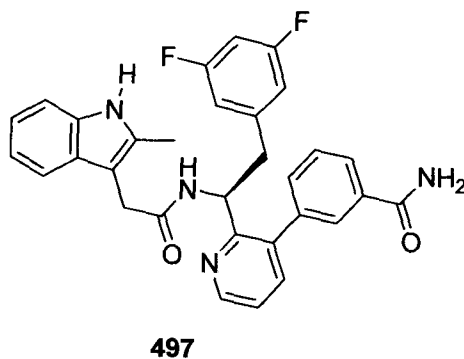
5

Synthesis of (S)-tert-butyl 3-(2-(1-(3-(3-carbamoylphenyl)pyridin-2-yl)-2-(3,5-difluorophenyl)ethylamino)-2-oxoethyl)-1H-indol-5-ylcarbamate (**496B**):

The title compound was prepared according to the method presented in the synthesis of **50D** utilizing **50C** and 2-(5-(tert-butoxycarbonylamino)-1H-indol-3-yl)acetic acid to provide 11 mg of the desired compound in a 16 % yield: ^1H NMR (400 MHz, dmsO) δ 10.65 (s, 1H), 8.93 (s, 1H), 8.62 (d, 1H), 8.51 (d, 1H), 7.96 (s, 1H), 7.85 (d, 1H), 7.68 (s, 1H), 7.58 (d, 2H), 7.43 (t, 1H), 7.37 (t, 3H), 7.14 (d, 1H), 6.97 (s, 2H), 6.84 (t, 1H), 6.37 (d, 2H), 5.22 (d, 1H), 3.43 (s, 2H), 2.94 (d, 2H), 1.42 (s, 9H); MS (m/z) 626.2 $[M+H]^+$.

10

15 Example 497

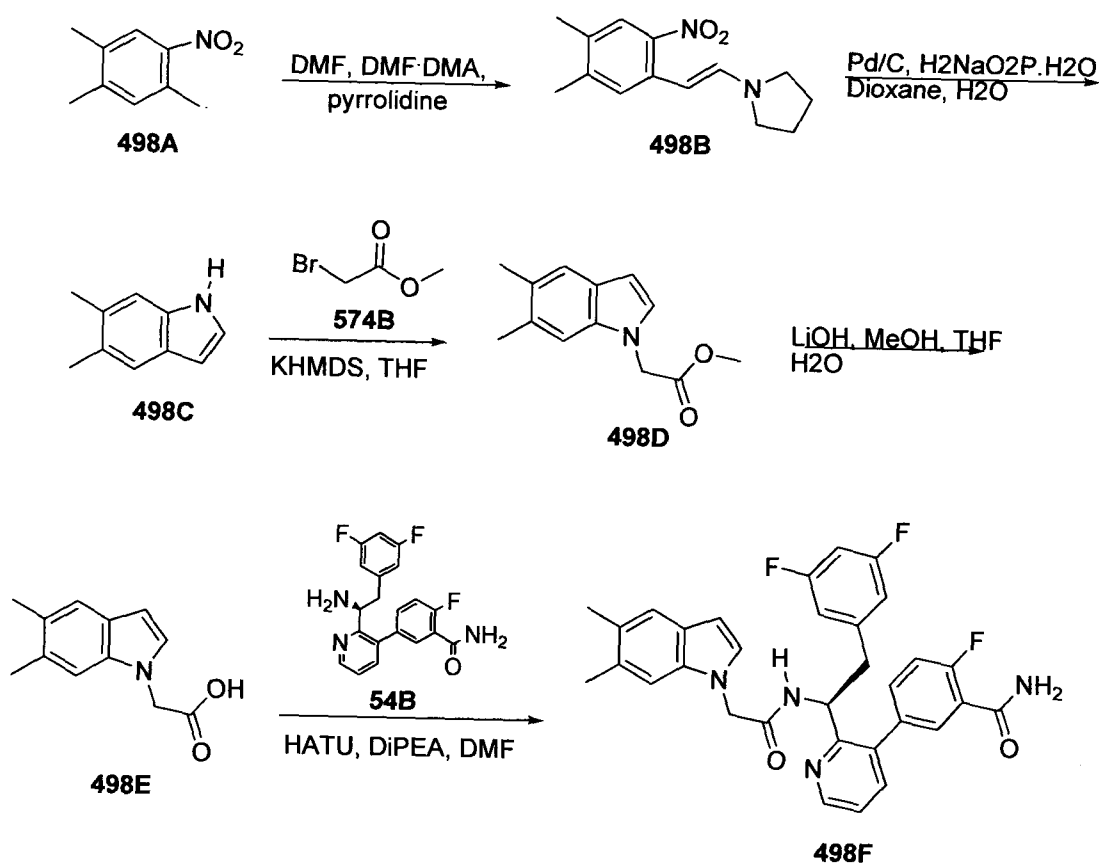


Synthesis of (S)-3-(2-(2-(3,5-difluorophenyl)-1-(2-(2-methyl-1H-indol-3-yl)acetamido)ethyl)pyridin-3-yl)benzamide (**497**):

The title compound was prepared according to the method presented in the synthesis of **50D** utilizing **50C** and 2-(2-methyl-1H-indol-3-yl)acetic acid to provide 22 mg of the desired

5 compound in a 37 % yield: ^1H NMR (400 MHz, dmso) δ 10.63 (s, 1H), 8.64 (dd, 1H), 8.51 (d, 1H), 7.94 (s, 1H), 7.86 (d, 1H), 7.76 (s, 1H), 7.61 (dd, 1H), 7.44 (d, 2H), 7.39 (dd, 2H), 7.19 (d, 1H), 7.12 (d, 1H), 6.98 – 6.84 (m, 2H), 6.76 (t, 1H), 6.50 (d, 2H), 5.14 (dd, 1H), 3.39 (q, 2H), 2.93 (d, 2H), 2.18 (s, 3H); MS (m/z) 525.4 $[\text{M}+\text{H}]^+$.

10 Example 498



Synthesis of 1-(4,5-dimethyl-2-nitrostyryl)pyrrolidine (**498B**):

The title compound was prepared according to the method presented in Example **536** substituting 1,2,4-trimethyl-5-nitrobenzene for **536C** to provide the desired compound.

15

Synthesis of 5,6-dimethyl-1H-indole (**498C**):

The title compound was prepared according to the method presented in Example **536** substituting 1-(4,5-dimethyl-2-nitrostyryl)pyrrolidine for **536D** to provide the desired compound: MS (m/z) 146.4 $[\text{M}+\text{H}]^+$.

Synthesis of methyl 2-(5,6-dimethyl-1H-indol-1-yl)acetate (**498D**):

The title compound was prepared according to the method presented in Example 478 substituting methyl 2-bromoacetate for **478B** and 5,6-dimethyl-1H-indole for **478A** to provide the desired compound: MS (m/z) 218.2 $[M+H]^+$.

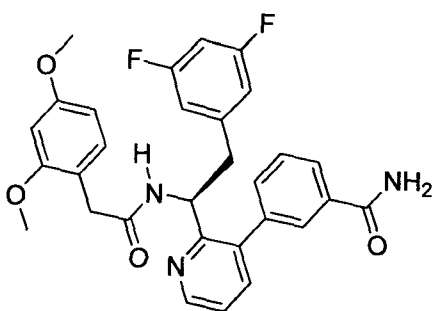
Synthesis of 2-(5,6-dimethyl-1H-indol-1-yl)acetic acid (**498E**):

The title compound was prepared according to the method presented in Example 478 substituting methyl 2-(5,6-dimethyl-1H-indol-1-yl)acetate for **478C** to provide the desired compound: MS (m/z) 204.2 $[M+H]^+$.

Synthesis of (S)-5-(2-(2-(3,5-difluorophenyl)-1-(2-(5,6-dimethyl-1H-indol-1-yl)acetamido)ethyl)pyridin-3-yl)-2-fluorobenzamide (**498F**):

The title compound was prepared according to the method presented in the synthesis of **54G** substituting 2-(5,6-dimethyl-1H-indol-1-yl)acetic acid for **54F** to provide the desired compound (5 mg, 9 %): ^1H NMR (400 MHz, dmsO) δ 8.83 (d, 1H), 8.67 (d, 1H), 7.69 – 7.56 (m, 3H), 7.47 (d, 1H), 7.40 (dd, 2H), 7.30 – 7.22 (m, 1H), 7.20 (s, 1H), 7.00 (d, 1H), 6.92 (t, 1H), 6.84 (s, 1H), 6.58 (d, 2H), 6.17 (d, 1H), 5.12 (d, 1H), 4.68 (s, 2H), 3.00 (d, 2H), 2.19 (d, 6H); MS (m/z) 557.6 $[M+H]^+$.

Example 499



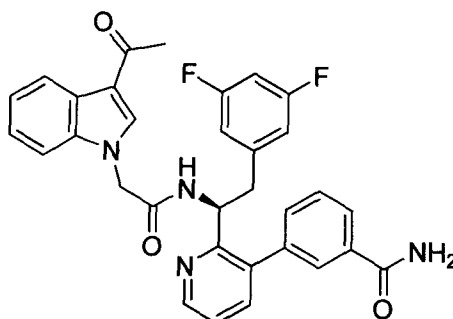
499

Synthesis of (S)-3-(2-(2-(3,5-difluorophenyl)-1-(2-(2,4-dimethoxyphenyl)acetamido)ethyl)pyridin-3-yl)benzamide (**499**):

The title compound was prepared according to the method presented in the synthesis of **50D** utilizing **50C** and 2-(2,4-dimethoxyphenyl)acetic acid to provide 21 mg of the desired compound in a 40 % yield: ^1H NMR (400 MHz, dmsO) δ 8.65 (d, 1H), 8.30 (d, 1H), 7.94 (s, 1H), 7.88 (d, 1H), 7.74 (s, 1H), 7.66 – 7.59 (m, 1H), 7.48 (t, 1H), 7.45 – 7.35 (m, 3H), 6.91 (t, 1H),

6.81 (d, 1H), 6.46 (d, 2H), 6.42 (d, 1H), 6.33 (dd, 1H), 5.23 – 5.13 (m, 1H), 3.68 (s, 3H), 3.59 (s, 3H), 3.24 (s, 2H), 2.92 (d, 2H); MS (m/z) 532.2[M+H]⁺.

Example 500

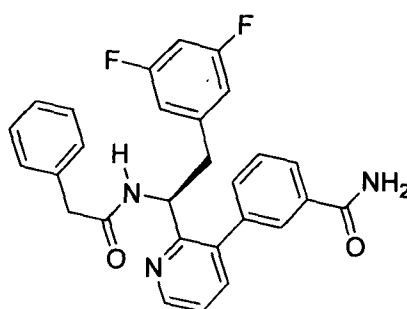


500

Synthesis of (S)-3-(2-(1-(2-(3-acetyl-1H-indol-1-yl)acetamido)-2-(3,5-difluorophenyl)ethyl)pyridin-3-yl)benzamide (**500**):

The title compound was prepared according to the method presented in the synthesis of **50D** utilizing **50C** and 2-(3-acetyl-1H-indol-1-yl)acetic acid to provide 22.6 mg of the desired compound in a 37% yield: ¹H NMR (400 MHz, dmso) δ 9.11 (d, 1H), 8.72 (dd, 1H), 8.09 (d, 2H), 7.94 (s, 1H), 7.87 (d, 1H), 7.74 (s, 1H), 7.65 (dd, 1H), 7.49 – 7.34 (m, 4H), 7.11 (td, 2H), 7.03 (s, 1H), 6.96 (t, 1H), 6.60 (d, 2H), 5.18 (dd, 1H), 4.86 (s, 2H), 3.09 – 2.96 (m, 2H), 2.35 (s, 3H); MS (m/z) 553.34 [M+H]⁺.

Example 501



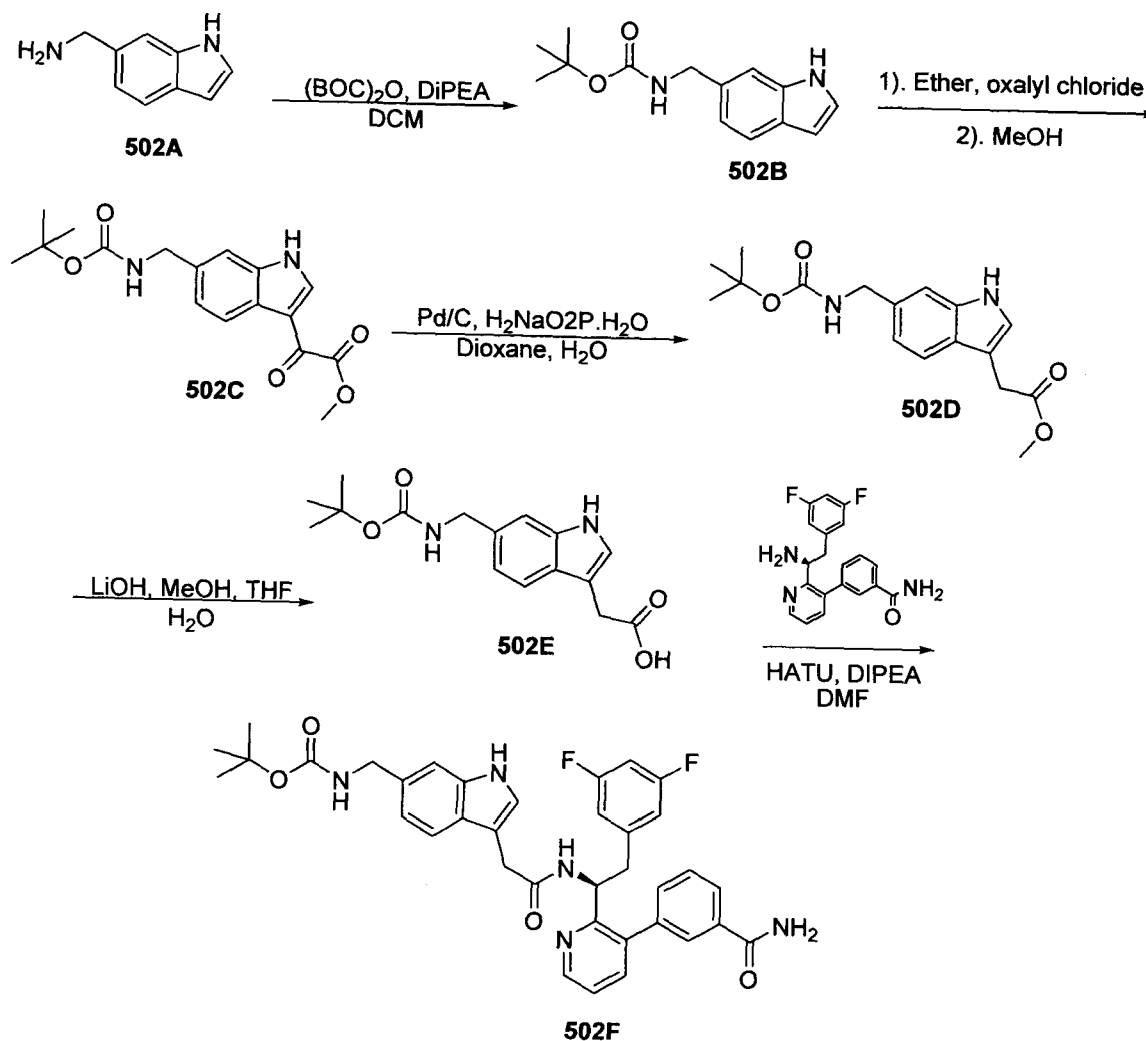
501

Synthesis of (S)-3-(2-(2-(3,5-difluorophenyl)-1-(2-phenylacetamido)ethyl)pyridin-3-yl)benzamide (**501**):

The title compound was prepared according to the method presented in the synthesis of **50D** utilizing **50C** and 2-phenylacetic acid to provide 21 mg of the desired compound in a 40 %

yield: ^1H NMR (400 MHz, dmso) δ 8.72 (d, 1H), 8.66 (d, 1H), 7.95 (s, 1H), 7.88 (d, 1H), 7.76 (s, 1H), 7.62 (d, 1H), 7.43 (ddd, 4H), 7.18 – 7.10 (m, 3H), 7.04 (d, 2H), 6.89 (t, 1H), 6.51 (d, 2H), 5.15 (d, 1H), 3.42 (d, 1H), 3.28 (d, 1H), 2.96 (d, 2H); MS (m/z) 472.3 $[\text{M}+\text{H}]^+$.

5 Example 502



Synthesis of ethyl tert-butyl (1H-indol-6-yl)methylcarbamate (**502B**):

The title compound was prepared according to the method presented in Example 491

10 substituting (1H-indol-6-yl)methanamine for ethyl **491A** to provide the desired compound: MS (m/z) 246.7 $[\text{M}+\text{H}]^+$.

Synthesis of methyl 2-(6-((tert-butoxycarbonylamino)methyl)-1H-indol-3-yl)-2-oxoacetate (**502C**):

The title compound was prepared according to the method presented in Example 491 substituting tert-butyl (1H-indol-6-yl)methylcarbamate for **491B** to provide the desired compound: MS (m/z) 333.9 $[M+H]^+$.

Synthesis of methyl 2-(6-((tert-butoxycarbonylamino)methyl)-1H-indol-3-yl)acetate (**502D**):

- 5 The title compound was prepared according to the method presented in Example 491 substituting methyl 2-(6-((tert-butoxycarbonylamino)methyl)-1H-indol-3-yl)-2-oxoacetate for **491C** to provide the desired compound: MS (m/z) 319.0 $[M+H]^+$.

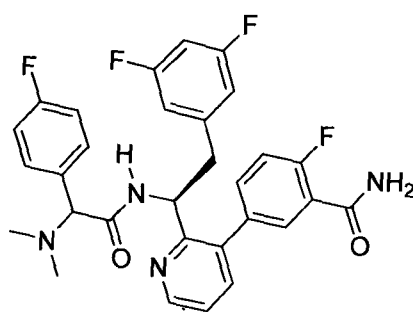
Synthesis of 2-(6-((tert-butoxycarbonylamino)methyl)-1H-indol-3-yl)acetic acid (**502E**):

- 10 The title compound was prepared according to the method presented in Example 491 substituting ethyl methyl 2-(6-((tert-butoxycarbonylamino)methyl)-1H-indol-3-yl)acetate for **491D** to provide the desired compound: MS (m/z) 304.9 $[M+H]^+$.

Synthesis of (S)-tert-butyl (3-(2-(1-(3-(3-carbamoylphenyl)pyridin-2-yl)-2-(3,5-difluorophenyl)ethylamino)-2-oxoethyl)-1H-indol-6-yl)methylcarbamate (**502F**):

- 15 The title compound was prepared according to the method presented in the synthesis of **50D** utilizing **50C** and 2-(6-((tert-butoxycarbonylamino)methyl)-1H-indol-3-yl)acetic acid to provide 30 mg of the desired compound in a 44 % yield: ^1H NMR (400 MHz, dmsO) δ 10.69 (s, 1H), 8.66 – 8.62 (m, 1H), 8.54 (d, 1H), 7.93 (s, 1H), 7.86 (d, 1H), 7.73 (s, 1H), 7.63 – 7.56 (m, 1H), 7.48 – 7.35 (m, 4H), 7.27 (s, 1H), 7.21 (d, 1H), 7.12 (s, 1H), 6.96 (s, 1H), 6.88 (t, 1H), 6.75 (d, 1H), 6.47 (d, 2H), 5.19 (d, 1H), 4.12 (d, 2H), 3.44 (d, 2H), 2.94 (d, 2H), 1.36 (s, 9H); MS (m/z) 640.2 $[M+H]^+$.
- 20

Example 503

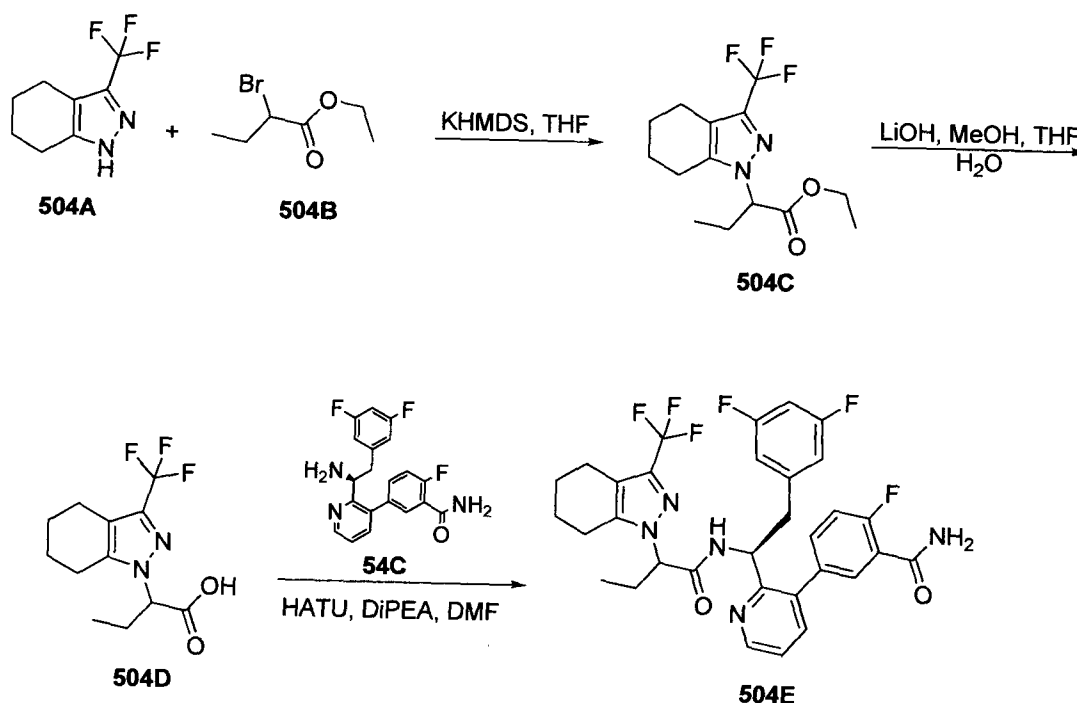


503

25 Synthesis of 5-(2-((1S)-2-(3,5-difluorophenyl)-1-(2-(dimethylamino)-2-(4-fluorophenyl)acetamido)ethyl)pyridin-3-yl)-2-fluorobenzamide (**503**):

The title compound was prepared according to the method presented in the synthesis of **54G** substituting 2-(dimethylamino)-2-(4-fluorophenyl)acetic acid for **54F** to provide the desired compound (the first peak off HPLC, 3 mg, 4 %): ^1H NMR (400 MHz, dmsO) δ 10.07 – 9.97 (m, 1H), 9.51 – 9.44 (m, 1H), 8.45 (s, 1H), 7.72 (s, 2H), 7.58 (d, 1H), 7.49 (d, 1H), 7.38 – 7.21 (m, 6H), 6.98 (s, 1H), 6.68 (d, 2H), 5.26 (s, 1H), 4.80 (s, 1H), 3.07 (s, 2H), 2.49 (s, 3H), 2.30 (s, 3H); MS (m/z) 551.3 $[\text{M}+\text{H}]^+$.

Example 504



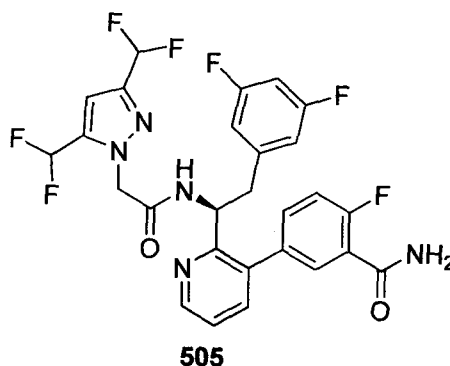
- 10 Synthesis of ethyl 2-(3-(trifluoromethyl)-4,5,6,7-tetrahydro-1H-indazol-1-yl)butanoate (**504C**):
A RB was charged with 3-(trifluoromethyl)-4,5,6,7-tetrahydro-1H-indazole (1 g, 5 mmol),
KHMDS (1.3 g, 7 mmol), and THF (5 ml). The resulting mixture was stirred for 10 minutes then
ethyl 2-bromobutanoate (0.7 mg, 5 mmol) was added. The mixture was stirred until done by
LC/MS then diluted with H_2O and extracted 2X EtOAc. The organic layers were dried over
15 sodium sulfate, and concentrated to afford the desired compound which was used crude in the
next reaction; MS (m/z) 305.3 $[\text{M}+\text{H}]^+$.

- Synthesis of 2-(3-(trifluoromethyl)-4,5,6,7-tetrahydro-1H-indazol-1-yl)butanoic acid (**504D**):
The title compound was prepared according to the method presented in Example **54** substituting
ethyl 2-(3-(trifluoromethyl)-4,5,6,7-tetrahydro-1H-indazol-1-yl)butanoate for **54E** to provide the
20 desired compound: MS (m/z) 277.3 $[\text{M}+\text{H}]^+$.

Synthesis of 5-(2-((1S)-2-(3,5-difluorophenyl)-1-(2-(3-(trifluoromethyl)-4,5,6,7-tetrahydro-1H-indazol-1-yl)butanamido)ethyl)pyridin-3-yl)-2-fluorobenzamide (**504E**):

The title compound was prepared according to the method presented in the synthesis of **54G** substituting 2-(3-(trifluoromethyl)-4,5,6,7-tetrahydro-1H-indazol-1-yl)butanoic acid for **54F** to provide the desired compound (24 mg, 28%): MS (m/z) 631.3 $[M+H]^+$.

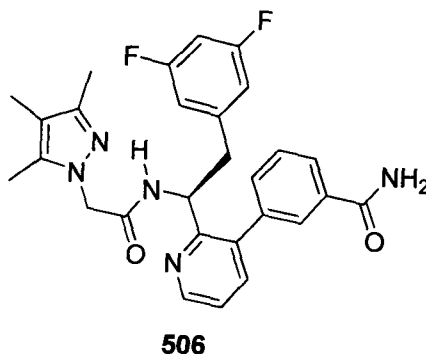
Example 505



Synthesis of (S)-5-(2-(1-(2-(3,5-bis(difluoromethyl)-1H-pyrazol-1-yl)acetamido)-2-(3,5-difluorophenyl)ethyl)pyridin-3-yl)-2-fluorobenzamide (**505**):

The title compound was prepared according to the method presented in the synthesis of **56B** substituting 3,5-bis(difluoromethyl)-1H-pyrazole for 1H-benzo[g]indole to provide the desired compound (25 mg, 62 %): ^1H NMR (400 MHz, dmso) δ 9.01 (d, 1H), 8.68 (dd, 1H), 7.68 – 7.57 (m, 3H), 7.41 (dd, 2H), 7.38 (d, 1H), 7.33 – 7.24 (m, 1H), 7.11 (d, 1H), 6.97 (d, 1H), 6.89 (d, 1H), 6.80 (d, 1H), 6.51 (d, 2H), 5.21 – 5.10 (m, 1H), 4.94 (s, 2H), 2.98 (dd, 2H); MS (m/z) 579.3 $[M+H]^+$.

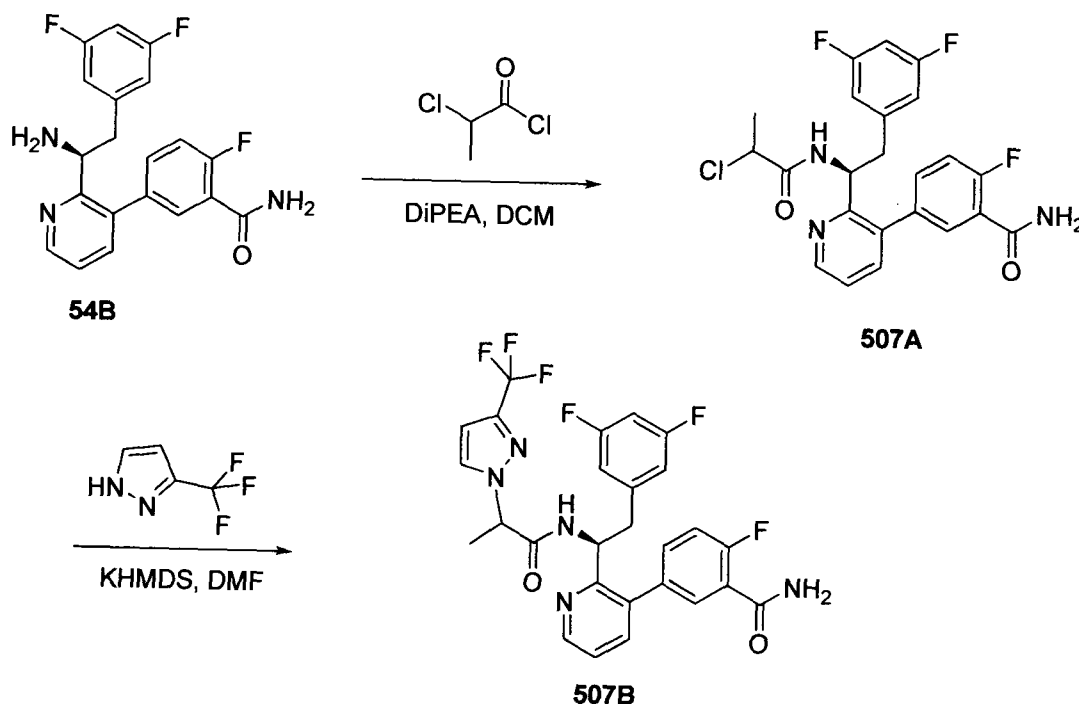
Example 506



Synthesis of (S)-3-(2-(2-(3,5-difluorophenyl)-1-(2-(3,4,5-trimethyl-1H-pyrazol-1-yl)acetamido)ethyl)benzamido)pyridin-3-yl)benzamide (**506**):

The title compound was prepared according to the method presented in the synthesis of **50D** utilizing **50C** and 2-(3,4,5-trimethyl-1H-pyrazol-1-yl)acetic acid to provide 21 mg of the desired compound in a 40 % yield: ^1H NMR (400 MHz, dmsO) δ 8.67 (dd, 2H), 7.94 (s, 1H), 7.89 (d, 1H), 7.72 (s, 1H), 7.65 (dd, 1H), 7.48 (t, 1H), 7.45 – 7.38 (m, 3H), 6.91 (t, 1H), 6.48 (d, 2H), 5.18 (dd, 1H), 4.60 (s, 2H), 3.04 – 2.88 (m, 2H), 1.99 (s, 3H), 1.87 (s, 3H), 1.78 (s, 3H); MS (m/z) 504.2 $[\text{M}+\text{H}]^+$.

Example 507



- 10 Synthesis of 5-(2-((1S)-1-(2-chloropropanamido)-2-(3,5-difluorophenyl)ethyl)pyridin-3-yl)-2-fluorobenzamide (**507A**):

The title compound was prepared according to the method presented in Example **56** substituting 2-chloropropanoyl chloride for 2-chloroacetyl chloride to provide the desired compound: MS (m/z) 462.9 $[\text{M}+\text{H}]^+$.

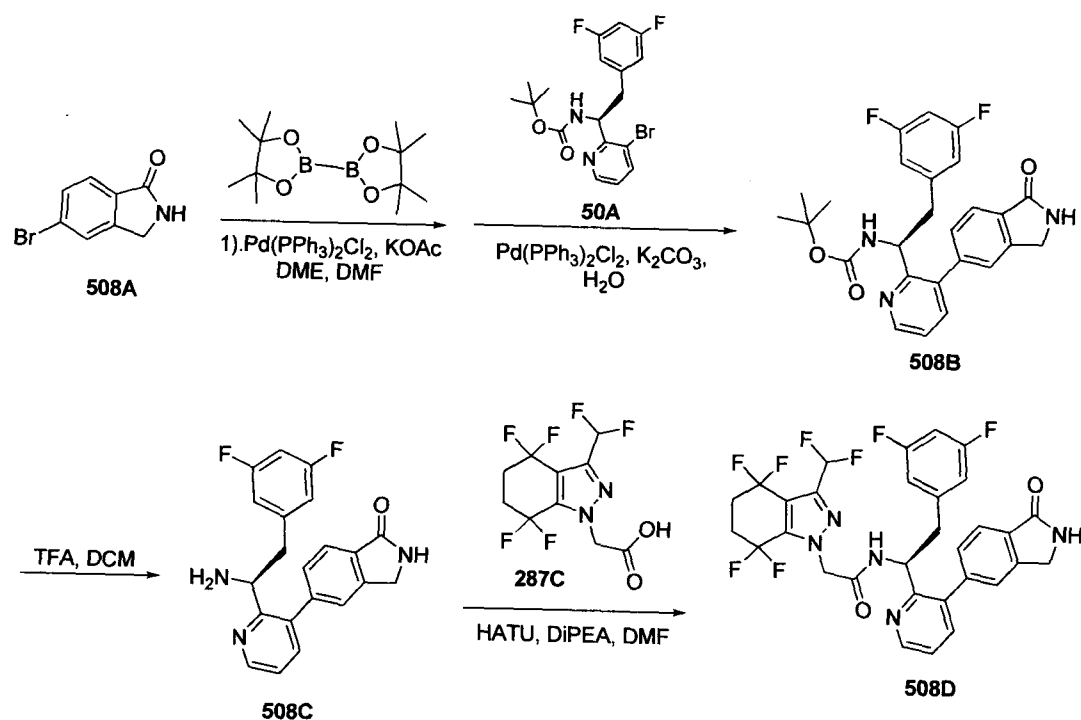
15

Synthesis of 5-(2-((1S)-2-(3,5-difluorophenyl)-1-(2-(3-(trifluoromethyl)-1H-pyrazol-1-yl)propanamido)ethyl)pyridin-3-yl)-2-fluorobenzamide (**507B**):

The title compound was prepared according to the method presented in the synthesis of **56B** substituting 3-(trifluoromethyl)-1H-pyrazole for 1H-benzo[g]indole and **507A** for **56A** to provide the desired compound (27 mg, 80 %): MS (m/z) 562.3 $[\text{M}+\text{H}]^+$.

20

Example 508



Synthesis of (S)-tert-butyl 2-(3,5-difluorophenyl)-1-(3-(1-oxoisindolin-5-yl)pyridin-2-yl)ethylcarbamate (**508B**):

- 5 The title compound was prepared according to the method presented in the synthesis of **489B** substituting 5-bromoisindolin-1-one for **489A** to provide the desired compound: MS (m/z) 466.2 $[\text{M}+\text{H}]^+$.

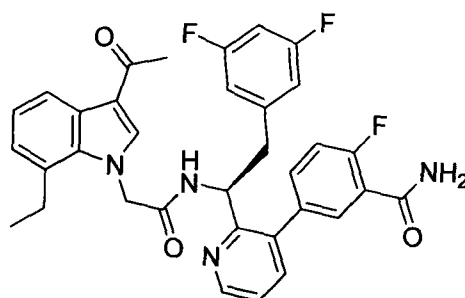
Synthesis of (S)-5-(2-(1-amino-2-(3,5-difluorophenyl)ethyl)pyridin-3-yl)isindolin-1-one (**508C**):

- 10 The title compound was prepared according to the method presented in the synthesis of **50C** substituting of (S)-tert-butyl 2-(3,5-difluorophenyl)-1-(3-(1-oxoisindolin-5-yl)pyridin-2-yl)ethylcarbamate for **50B** to provide the desired compound: MS (m/z) 366.1 $[\text{M}+\text{H}]^+$.

15 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-(3-(1-oxoisindolin-5-yl)pyridin-2-yl)ethyl)acetamide (**508D**):

- The title compound was prepared according to the method presented in the synthesis of **61F** substituting **287C** for **61C** and **508C** for **61E** to provide the desired compound (34 mg): ^1H NMR (400 MHz, cd_3od) δ 8.78 – 8.68 (m, 1H), 7.76 (d, 1H), 7.63 (dd, 1H), 7.43 (dd, 1H), 7.15 (s, 2H), 6.87 (d, 1H), 6.75 – 6.63 (m, 1H), 6.26 (d, 2H), 5.43 – 5.32 (m, 1H), 5.08 (s, 2H), 4.42 (q, 2H), 3.16 – 2.93 (m, 3H), 2.66 – 2.39 (m, 4H); MS (m/z) 650.4 $[\text{M}+\text{H}]^+$.
- 20

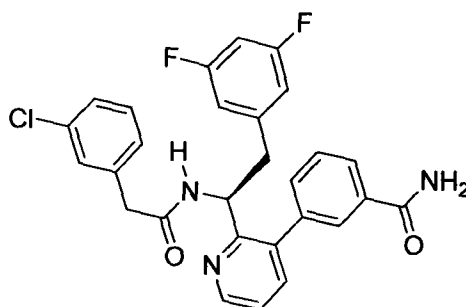
Example 509

**509**

Synthesis of (S)-5-(2-(1-(2-(3-acetyl-7-ethyl-1H-indol-1-yl)acetamido)-2-(3,5-difluorophenyl)ethyl)pyridin-3-yl)-2-fluorobenzamide (**509**):

The title compound was prepared according to the method presented in the synthesis of **54G** utilizing **54B** and 2-(3-acetyl-7-ethyl-1H-indol-1-yl)acetic acid to provide 15 mg of the desired compound in a 18 % yield: ^1H NMR (400 MHz, dmsO) δ 9.10 (d, 1H), 8.69 (dd, 1H), 8.12 (s, 1H), 8.01 (d, 1H), 7.64 (s, 2H), 7.60 (dd, 1H), 7.52 – 7.48 (m, 1H), 7.41 (dd, 2H), 7.32 – 7.24 (m, 1H), 7.07 – 6.92 (m, 2H), 6.86 (d, 1H), 6.63 (d, 2H), 5.14 (dd, 1H), 4.98 (s, 2H), 3.02 (d, 2H), 2.52 (dd, 3H), 2.33 (s, 3H); MS (m/z) 599.7 $[\text{M}+\text{H}]^+$.

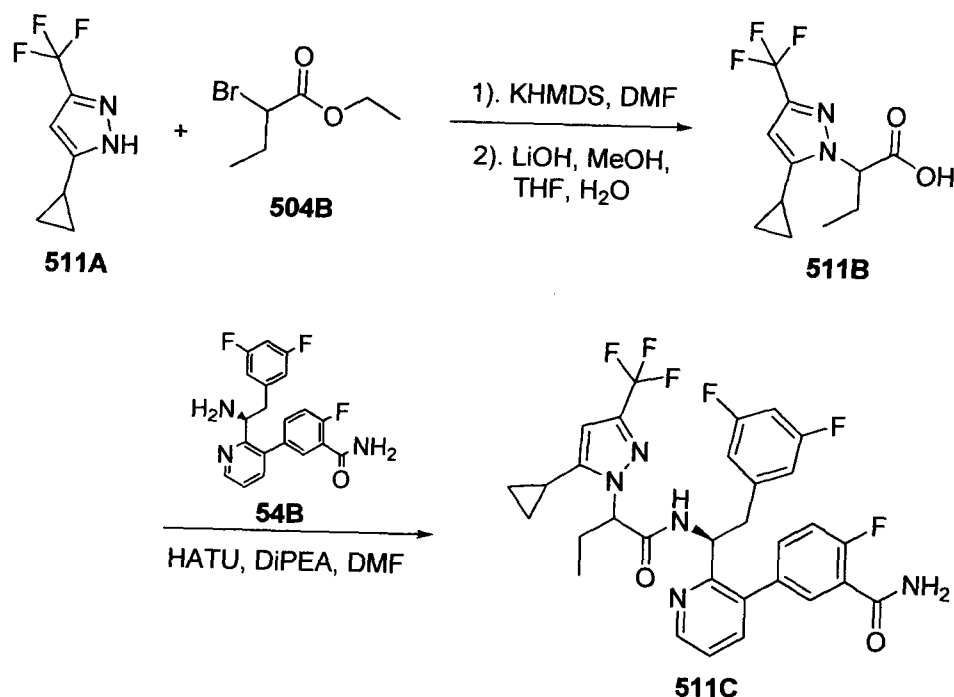
Example 510

**510**

Synthesis of (S)-3-(2-(1-(2-(3-chlorophenyl)acetamido)-2-(3,5-difluorophenyl)ethyl)pyridin-3-yl)benzamide (**510**):

The title compound was prepared according to the method presented in the synthesis of **50D** utilizing **50C** and 2-(3-chlorophenyl)acetic acid to provide 18 mg of the desired compound in a 40 % yield: ^1H NMR (400 MHz, dmsO) δ 8.79 (d, 1H), 8.67 (dd, 1H), 7.95 (s, 1H), 7.89 (d, 1H), 7.76 (s, 1H), 7.63 (dd, 1H), 7.44 (ddd, 4H), 7.19 (d, 2H), 7.11 (s, 1H), 7.01 (d, 1H), 6.88 (t, 1H), 6.50 (d, 2H), 5.15 (dd, 1H), 3.37 (dd, 2H), 2.96 (d, 2H); MS (m/z) 506.6 $[\text{M}+\text{H}]^+$.

Example 511



Synthesis of ethyl 2-(5-cyclopropyl-3-(trifluoromethyl)-1H-pyrazol-1-yl)butanoate:

The title compound was prepared according to the method presented in Example 478 substituting **504B** for **478B** to provide the desired compound: MS (m/z) 291.1 $[\text{M}+\text{H}]^+$.

5

Synthesis of 2-(5-cyclopropyl-3-(trifluoromethyl)-1H-pyrazol-1-yl)butanoic acid (**511B**):

The title compound was prepared according to the method presented in Example 478 substituting ethyl 2-(5-cyclopropyl-3-(trifluoromethyl)-1H-pyrazol-1-yl)butanoate for **478C** to provide the desired compound: MS (m/z) 263.1 $[\text{M}+\text{H}]^+$.

10

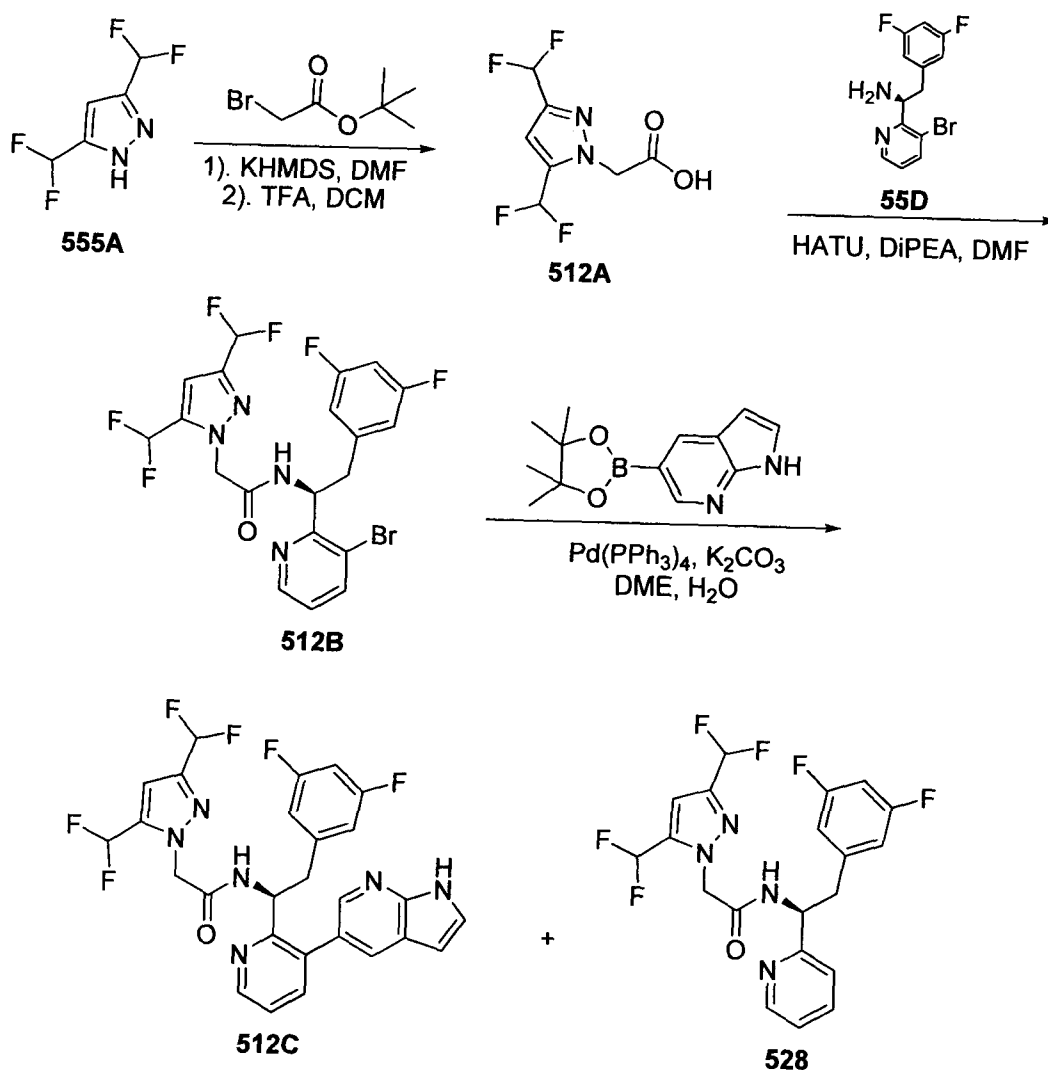
Synthesis of 5-(2-((1S)-1-(2-(5-cyclopropyl-3-(trifluoromethyl)-1H-pyrazol-1-yl)butanamido)-2-(3,5-difluorophenyl)ethyl)pyridin-3-yl)-2-fluorobenzamide (**511C**):

The title compound was prepared according to the method presented in the synthesis of **54G** substituting 2-(5-cyclopropyl-3-(trifluoromethyl)-1H-pyrazol-1-yl)butanoic acid for 2-(5-

(trifluoromethyl)-1H-indol-3-yl)acetic acid to provide the desired compound (32 mg, 39 %): MS (m/z) 616.4 $[\text{M}+\text{H}]^+$.

15

Examples 512 and 528



Synthesis of tert-butyl 2-(3,5-bis(difluoromethyl)-1H-pyrazol-1-yl)acetate:

The title compound was prepared according to the method presented in Example 478 substituting tert-butyl 2-bromoacetate for ethyl 2-bromo-3-methylbutanoate to provide the
5 desired compound: MS (m/z) 285.0 $[M+H]^+$.

Synthesis of 2-(3,5-bis(difluoromethyl)-1H-pyrazol-1-yl)acetic acid (512A):

A round bottom flask was charged with tert-butyl 2-(3,5-bis(difluoromethyl)-1H-pyrazol-1-yl)acetate (1.3 g, 4.6 mmol) and TFA:DCM 1:1 (4 ml). The reaction was stirred at room
10 temperature until done by LC/MS then concentrated 2X from DCM. The crude mixture was used as is in next reaction. MS (m/z) 227.0 $[M+H]^+$.

Synthesis of (S)-2-(3,5-bis(difluoromethyl)-1H-pyrazol-1-yl)-N-(1-(3-bromopyridin-2-yl)-2-(3,5-difluorophenyl)ethyl)acetamide (512B):

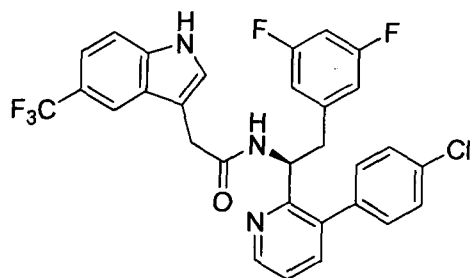
The title compound was prepared according to the method presented in the synthesis of **54G** substituting 2-(3,5-bis(difluoromethyl)-1H-pyrazol-1-yl)acetic acid for 2-(5-(trifluoromethyl)-1H-indol-3-yl)acetic acid and **55D** for **54B** to provide the desired compound: MS (m/z) 521.9 $[M+H]^+$.

5

Synthesis of (S)-N-(1-(3-(1H-pyrrolo[2,3-b]pyridin-5-yl)pyridin-2-yl)-2-(3,5-difluorophenyl)ethyl)-2-(3,5-bis(difluoromethyl)-1H-pyrazol-1-yl)acetamide (**512C**) and (S)-2-(3,5-bis(difluoromethyl)-1H-pyrazol-1-yl)-N-(2-(3,5-difluorophenyl)-1-(pyridin-2-yl)ethyl)acetamide (**528**):

- 10 A microwave vial was charged with **512B** (100 mg, 0.2 mmol), DMF (0.5 ml), DME (1.5 ml), 5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrrolo[2,3-b]pyridine (51 mg, 0.2 mmol), Pd(PPh₃)₄ (11 mg, 0.01 mmol) and K₂CO₃ (39 mg, 0.3 mmol) dissolved in water (0.3 ml). Microwave the mixture at 150 °C for 30 minutes. Allow the reaction to cool then dilute with H₂O and extract 2X EtOAc. The combined organic layers were washed with brine then dried
- 15 over sodium sulfate, concentrated, and purified by HPLC to give the desired compounds (**512C**, 5 mg, 5 %) and (**528**, 5 mg, 6 %): **512C** ¹H NMR (400 MHz, dmso) δ 11.76 (s, 1H), 8.96 (s, 1H), 8.68 (d, 1H), 7.95 (s, 1H), 7.64 (d, 2H), 7.50 (s, 1H), 7.46 – 7.37 (m, 1H), 7.11 (d, 1H), 6.97 (d, 2H), 6.80 (d, 1H), 6.41 (d, 3H), 5.19 (d, 1H), 4.96 (s, 2H), 3.05 (d, 1H), 2.97 (d, 1H); MS (m/z) 559.1 $[M+H]^+$; **528** ¹H NMR (400 MHz, dmso) δ 8.89 (d, 1H), 8.55 (d, 1H), 7.76 (t, 1H), 7.37 – 7.28 (m, 2H), 7.13 (d, 1H), 7.07 – 6.92 (m, 2H), 6.84 (dd, 4H), 5.13 (d, 1H), 4.97 (q, 2H), 3.17 (dd, 1H), 3.07 – 2.95 (m, 1H); MS (m/z) 443.0 $[M+H]^+$.
- 20

Example 513



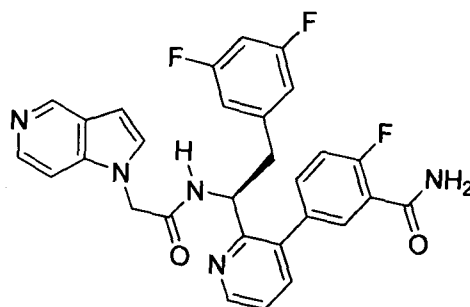
513

- 25 Synthesis of (S)-N-(1-(3-(4-chlorophenyl)pyridin-2-yl)-2-(3,5-difluorophenyl)ethyl)-2-(5-(trifluoromethyl)-1H-indol-3-yl)acetamide (**513**):

The title compound was prepared according to the method presented in the synthesis of **36F** utilizing **36E** and **54F** to provide 17.8 mg of the desired compound in a 30 % yield: ¹H NMR

(400 MHz, dmso) δ 11.25 (s, 1H), 8.67 (d, 1H), 8.63 (dd, 1H), 7.82 (s, 1H), 7.53 (dd, 1H), 7.46 (d, 1H), 7.36 (dd, 3H), 7.29 (d, 1H), 7.23 (d, 1H), 7.15 (d, 2H), 6.87 (t, 1H), 6.38 (d, 2H), 5.14 (q, 1H), 3.55 (s, 2H), 2.91 (t, 2H); MS (m/z) 570.1 $[M+H]^+$.

5 Example 514



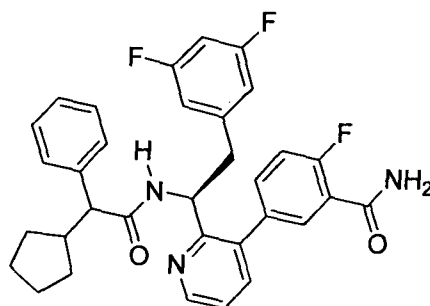
514

Synthesis of (S)-5-(2-(1-(2-(1H-pyrrolo[3,2-c]pyridin-1-yl)acetamido)-2-(3,5-difluorophenyl)ethyl)pyridin-3-yl)-2-fluorobenzamide (**514**):

The title compound was prepared according to the method presented in Example 56 substituting 1H-pyrrolo[3,2-c]pyridine for 1H-benzo[g]indole to provide the desired compound (23 mg, 62%): ^1H NMR (400 MHz, dmso) δ 9.21 (s, 1H), 9.12 (d, 1H), 8.72 (dd, 1H), 8.39 (d, 1H), 7.75 (d, 1H), 7.70 (d, 1H), 7.62 (dd, 3H), 7.52 – 7.46 (m, 1H), 7.43 (dd, 1H), 7.35 (s, 1H), 7.32 – 7.23 (m, 1H), 6.98 (d, 1H), 6.90 (t, 1H), 6.55 (d, 2H), 5.15 (dd, 1H), 5.07 (d, 2H), 3.10 – 2.96 (m, 2H); MS (m/z) 530.5 $[M+H]^+$.

15

Example 515



515

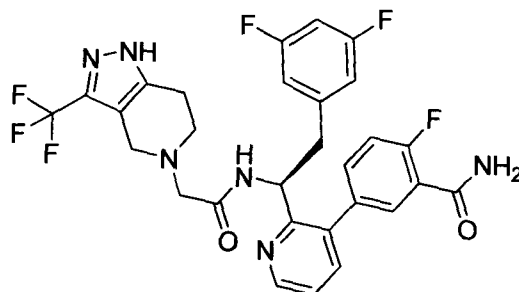
Synthesis of 5-(2-((1S)-1-(2-cyclopentyl-2-phenylacetamido)-2-(3,5-difluorophenyl)ethyl)pyridin-3-yl)-2-fluorobenzamide (**515**):

The title compound was prepared according to the method presented in the synthesis of **54G** substituting 2-cyclopentyl-2-phenylacetic acid for **54F** to provide the desired compound (the

second peak off HPLC, 12 mg, 16 %): ^1H NMR (400 MHz, dmso) δ 10.16 – 10.05 (m, 1H), 9.58 (s, 1H), 8.68 (d, 1H), 7.79 – 7.65 (m, 3H), 7.63 (s, 1H), 7.50 (s, 1H), 7.48 – 7.35 (m, 2H), 7.35 – 7.28 (m, 2H), 7.18 (t, 2H), 6.78 (s, 1H), 6.35 (d, 2H), 5.20 (s, 1H), 4.78 (s, 1H), 2.91 (d, 3H), 2.58 (s, 4H), 2.33 (s, 4H); MS (m/z) 558.6 $[\text{M}+\text{H}]^+$.

5

Example 516

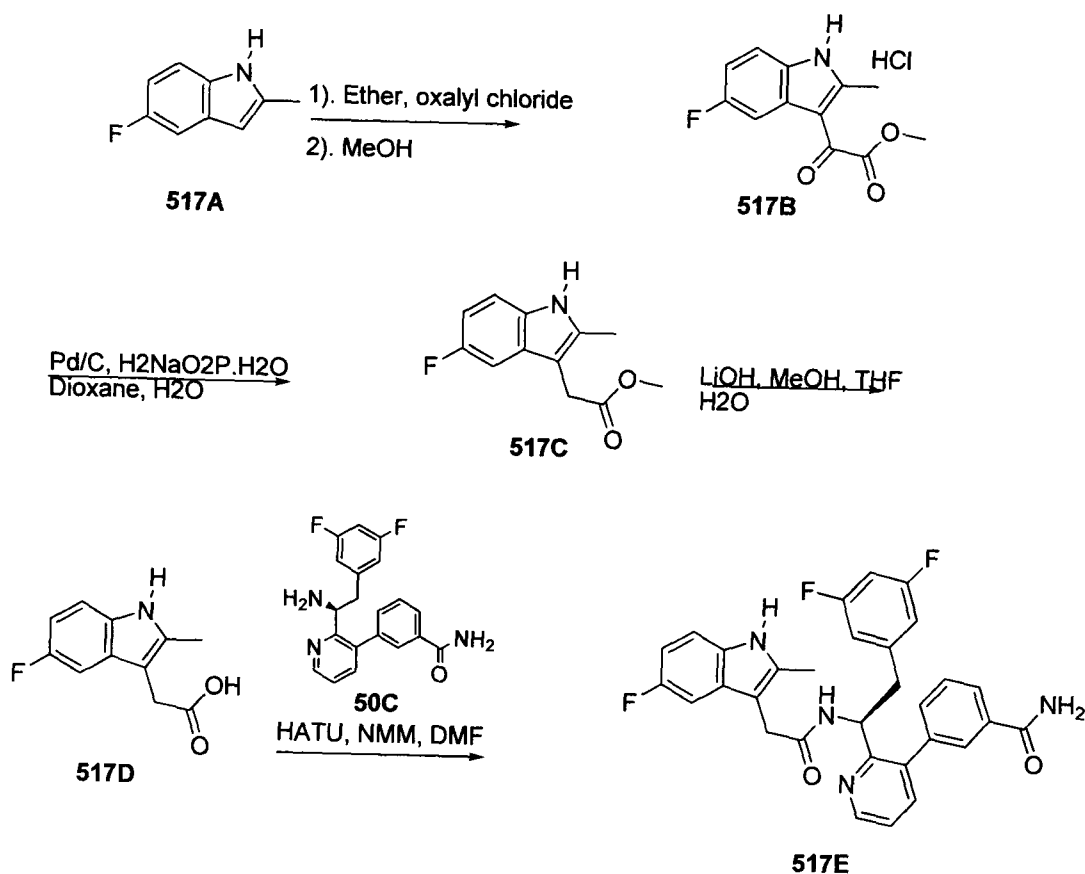


516

Synthesis of (S)-5-(2-(2-(3,5-difluorophenyl)-1-(2-(3-(trifluoromethyl)-6,7-dihydro-1H-pyrazolo[4,3-c]pyridin-5(4H)-yl)acetamido)ethyl)pyridin-3-yl)-2-fluorobenzamide (**516**):

- 10 The title compound was prepared according to the method presented in the synthesis of **56B** substituting 3-(trifluoromethyl)-4,5,6,7-tetrahydro-1H-pyrazolo[4,3-c]pyridine for 1H-benzo[g]indole to provide the desired compound (1 mg, 2 %): ^1H NMR (400 MHz, cd_3od) δ 8.71 (s, 1H), 7.57 (d, 1H), 7.55 – 7.49 (m, 1H), 7.40 (d, 1H), 7.21 (d, 2H), 6.72 – 6.62 (m, 1H), 6.35 (s, 2H), 5.32 (s, 1H), 4.29 (s, 2H), 3.48 (d, 2H), 3.17 – 3.00 (m, 4H), 2.99 – 2.89 (m, 2H); MS
- 15 (m/z) 603.3 $[\text{M}+\text{H}]^+$.

Example 517



Synthesis of methyl 2-(5-fluoro-2-methyl-1H-indol-3-yl)-2-oxoacetate hydrochloride (**517B**):

The title compound was prepared according to the method presented in Example **54** substituting 5-fluoro-2-methyl-1H-indole for **54C** to provide the desired compound: MS (*m/z*) 236.3

5 [M+H]⁺.

Synthesis methyl 2-(5-fluoro-2-methyl-1H-indol-3-yl)acetate (**517C**):

The title compound was prepared according to the method presented in Example **54** substituting of methyl 2-(5-fluoro-2-methyl-1H-indol-3-yl)-2-oxoacetate hydrochloride for **54D** to provide the desired compound: MS (*m/z*) 222.1 [M+H]⁺.

10

Synthesis of 2-(5-fluoro-2-methyl-1H-indol-3-yl)acetic acid (**517D**):

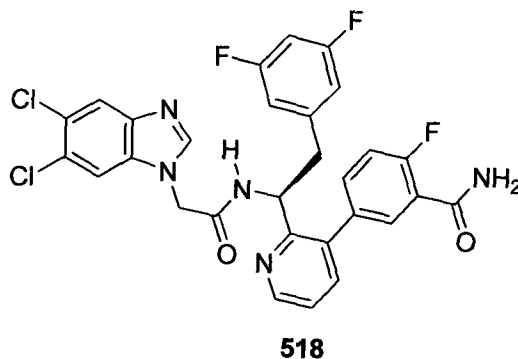
The title compound was prepared according to the method presented in Example **54** substituting methyl 2-(5-fluoro-2-methyl-1H-indol-3-yl)acetate for **54E** to provide the desired compound:

15 MS (*m/z*) 208.2 [M+H]⁺.

Synthesis of (S)-3-(2-(2-(3,5-difluorophenyl)-1-(2-(5-fluoro-2-methyl-1H-indol-3-yl)acetamido)ethyl)pyridin-3-yl)benzamide (**517E**):

The title compound was prepared according to the method presented in the synthesis of **50D** utilizing **50C** and 2-(5-fluoro-2-methyl-1H-indol-3-yl)acetic acid to provide 17 mg of the desired compound in a 27 % yield: ^1H NMR (400 MHz, dmso) δ 10.75 (s, 1H), 8.64 (dd, 1H), 8.59 (d, 1H), 7.94 (s, 1H), 7.87 (d, 1H), 7.75 (s, 1H), 7.60 (dd, 1H), 7.45 (d, 2H), 7.39 (dd, 2H), 7.10 (dd, 1H), 7.04 (dd, 1H), 6.86 (t, 1H), 6.76 – 6.65 (m, 1H), 6.47 (d, 2H), 5.13 (t, 1H), 3.43 – 3.30 (m, 2H), 2.93 (d, 2H), 2.18 (s, 3H); MS (m/z) 543.8 $[\text{M}+\text{H}]^+$.

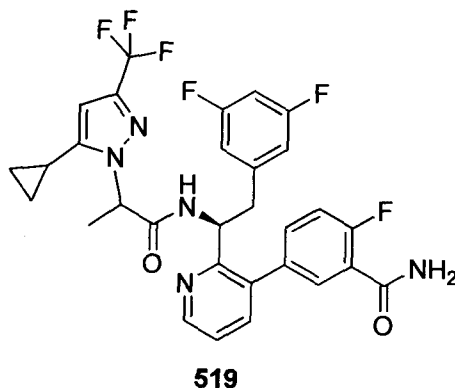
Example 518



- 10 Synthesis of (S)-5-(2-(1-(2-(5,6-dichloro-1H-benzo[d]imidazol-1-yl)acetamido)-2-(3,5-difluorophenyl)ethyl)pyridin-3-yl)-2-fluorobenzamide (**518**):

The title compound was prepared according to the method presented in Example **56** substituting 5,6-dichloro-1H-benzo[d]imidazole for 1H-benzo[g]indole to provide the desired compound (19 mg, 45%): ^1H NMR (400 MHz, dmso) δ 9.13 (d, 1H), 8.71 (d, 1H), 8.21 (s, 1H), 7.88 (s, 1H), 7.61 (dd, 3H), 7.53 (s, 1H), 7.47 (d, 1H), 7.44 – 7.35 (m, 2H), 7.31 – 7.23 (m, 1H), 6.89 (t, 1H), 6.55 (d, 2H), 5.20 – 5.10 (m, 1H), 4.92 (s, 2H), 3.02 (d, 2H); MS (m/z) 599.3 $[\text{M}+\text{H}]^+$.

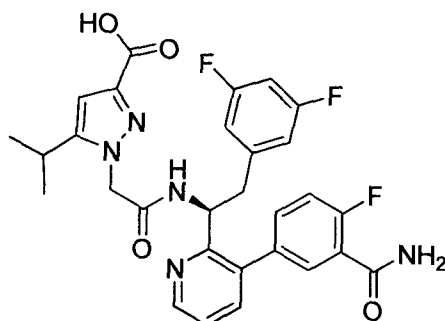
Example 519



- 20 Synthesis of 5-(2-((1S)-1-(2-(5-cyclopropyl-3-(trifluoromethyl)-1H-pyrazol-1-yl)propanamido)-2-(3,5-difluorophenyl)ethyl)pyridin-3-yl)-2-fluorobenzamide (**519**):

The title compound was prepared according to the method presented in the synthesis of **56B** substituting 5-cyclopropyl-3-(trifluoromethyl)-1H-pyrazole for 1H-benzo[g]indole and **507A** for **56A** to provide the desired compound (23 mg, 64 %): MS (m/z) 602.3 $[M+H]^+$.

5 Example 521

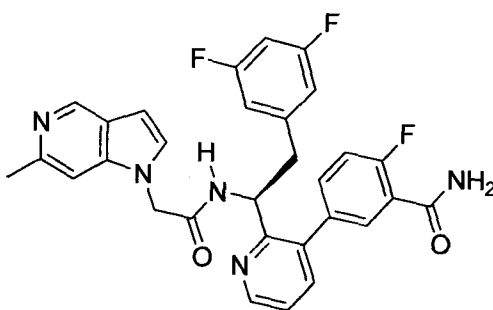


521

Synthesis of (S)-1-(2-(1-(3-(3-carbamoyl-4-fluorophenyl)pyridin-2-yl)-2-(3,5-difluorophenyl)ethylamino)-2-oxoethyl)-5-isopropyl-1H-pyrazole-3-carboxylic acid (**521**):

The title compound was prepared according to the method presented in the synthesis of **56B** substituting 5-isopropyl-1H-pyrazole-3-carboxylic acid for 1H-benzo[g]indole to provide the desired compound (2 mg, 5 %): ^1H NMR (400 MHz, dmso) δ 8.71 (d, 1H), 8.65 (d, 1H), 7.69 – 7.56 (m, 3H), 7.48 – 7.36 (m, 3H), 7.34 – 7.26 (m, 1H), 6.89 (t, 1H), 6.50 (d, 3H), 5.16 (d, 1H), 4.59 (s, 2H), 3.03 – 2.88 (m, 4H), 1.18 (d, 6H); MS (m/z) 566.4 $[M+H]^+$.

15 Example 522



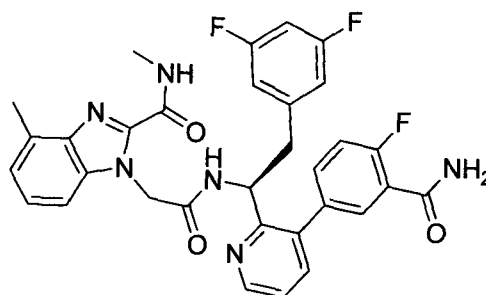
522

Synthesis of (S)-5-(2-(2-(3,5-difluorophenyl)-1-(2-(6-methyl-1H-pyrrolo[3,2-c]pyridin-1-yl)acetamido)ethyl)pyridin-3-yl)-2-fluorobenzamide (**522**):

The title compound was prepared according to the method presented in Example **56** substituting 6-methyl-1H-pyrrolo[3,2-c]pyridine for 1H-benzo[g]indole to provide the desired compound (9 mg, 24 %): ^1H NMR (400 MHz, dmso) δ 9.09 (d, 2H), 8.71 (d, 1H), 7.62 (dd, 4H), 7.54 (s, 1H),

7.49 (d, 1H), 7.43 (dd, 1H), 7.36 (s, 1H), 7.33 – 7.25 (m, 1H), 6.91 (s, 1H), 6.88 (d, 1H), 6.57 (d, 2H), 5.16 (s, 1H), 4.98 (d, 2H), 3.02 (d, 2H), 2.63 (s, 3H); MS (m/z) 544.5 $[M+H]^+$.

Example 523

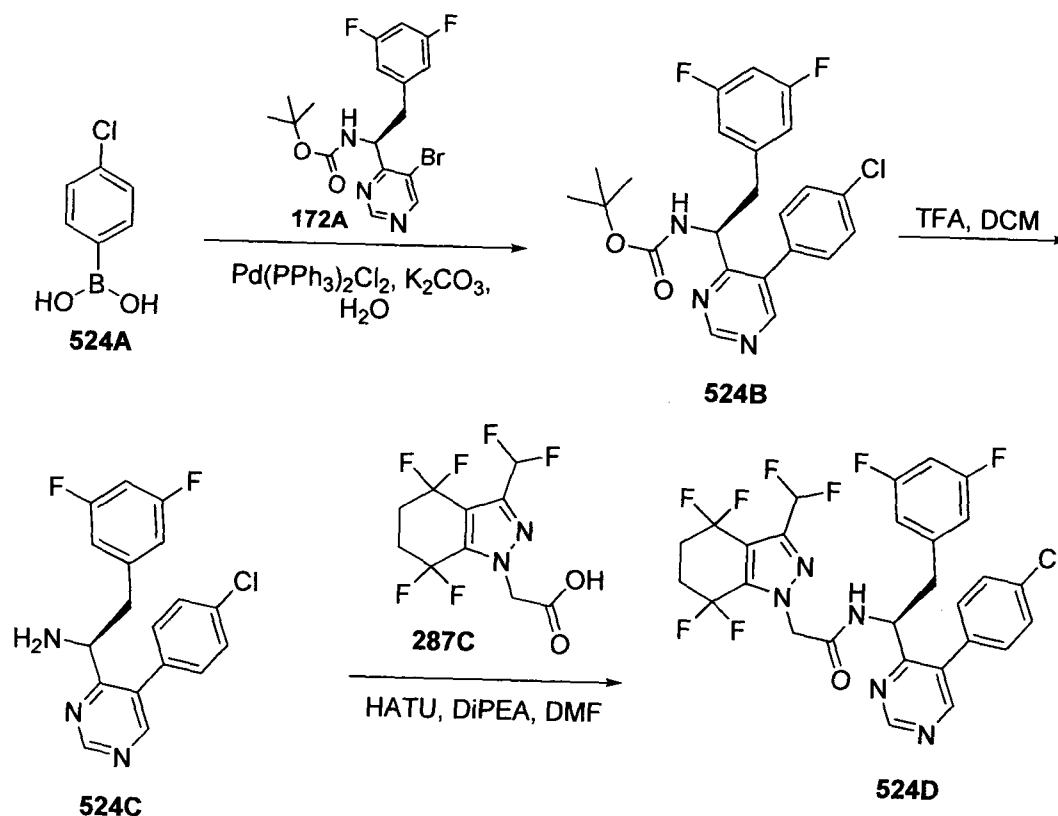


523

Synthesis of (S)-1-(2-(1-(3-(3-carbamoyl-4-fluorophenyl)pyridin-2-yl)-2-(3,5-difluorophenyl)ethylamino)-2-oxoethyl)-N,4-dimethyl-1H-benzo[d]imidazole-2-carboxamide (**523**):

The title compound was prepared according to the method presented in the synthesis of **54G** substituting 2-(4-methyl-2-(methylcarbamoyl)-1H-benzo[d]imidazol-1-yl)acetic acid for **54F** to provide the desired compound (24 mg, 37 %): ^1H NMR (400 MHz, dmso) δ 9.29 (d, 1H), 8.71 (dd, 1H), 8.25 (d, 1H), 7.72 (d, 1H), 7.69 – 7.60 (m, 3H), 7.54 – 7.48 (m, 1H), 7.48 – 7.35 (m, 4H), 7.33 – 7.24 (m, 1H), 6.93 (t, 1H), 6.60 (d, 2H), 5.21 – 5.07 (m, 4H), 4.01 (q, 2H), 3.02 (dd, 2H), 2.58 (d, 3H); MS (m/z) 601.4 $[M+H]^+$.

Example 524



Synthesis of (S)-tert-butyl 1-(5-(4-chlorophenyl)pyrimidin-4-yl)-2-(3,5-difluorophenyl)ethylcarbamate (**524B**):

- 5 The title compound was prepared according to the method presented in the synthesis of **489B** starting from step 2 and substituting 4-chlorophenylboronic acid for **489A** and **172A** for **50A** to provide the desired compound: MS (m/z) 446.5 $[\text{M}+\text{H}]^+$.

Synthesis of (S)-1-(5-(4-chlorophenyl)pyrimidin-4-yl)-2-(3,5-difluorophenyl)ethanamine (**524C**):

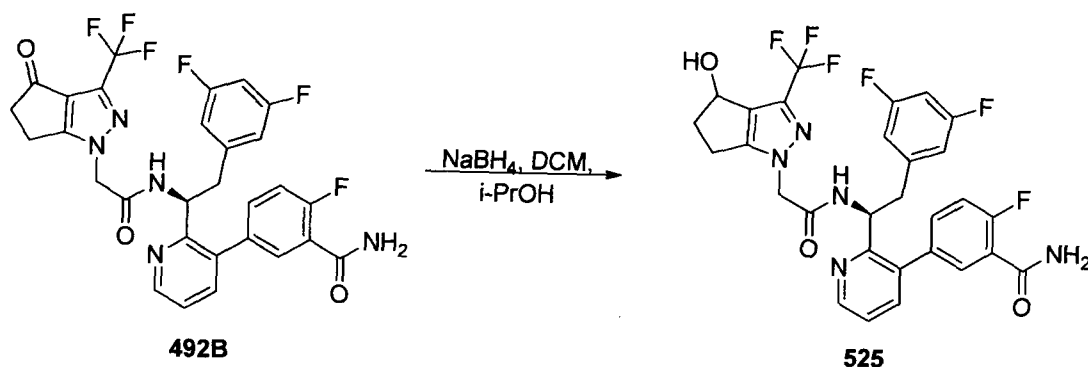
- 10 The title compound was prepared according to the method presented in the synthesis of **50C** substituting (S)-tert-butyl 1-(5-(4-chlorophenyl)pyrimidin-4-yl)-2-(3,5-difluorophenyl)ethylcarbamate for **50B** to provide the desired compound: MS (m/z) 346.3 $[\text{M}+\text{H}]^+$.

- 15 Synthesis of (S)-N-(1-(5-(4-chlorophenyl)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 (**524D**):

The title compound was prepared according to the method presented in the synthesis of **61F** substituting **287C** for **61C** and **524C** for **61E** to provide the desired compound (25 mg): ^1H NMR (400 MHz, cd_3od) δ 9.21 (s, 1H), 9.06 (d, 1H), 8.52 (s, 1H), 7.41 (d, 2H), 7.14 (d, 2H),

6.94 – 6.61 (m, 2H), 6.34 (d, 2H), 5.41 (q, 1H), 5.06 (s, 2H), 3.03 (d, 2H), 2.62 – 2.40 (m, 4H); MS (*m/z*) 630.7 [*M*+*H*]⁺.

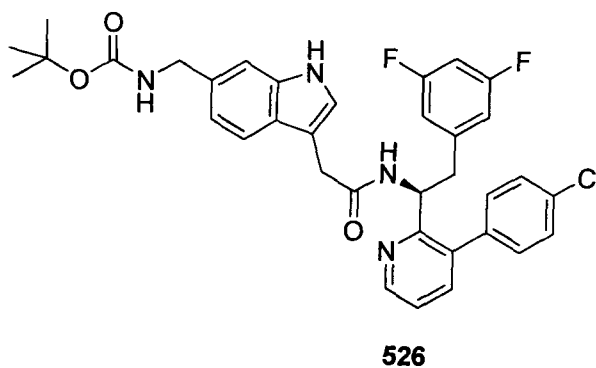
Example 525



Synthesis of 5-(2-((1*S*)-2-(3,5-difluorophenyl)-1-(2-(4-hydroxy-3-(trifluoromethyl)-5,6-dihydrocyclopenta[*c*]pyrazol-1(4*H*)-yl)acetamido)ethyl)pyridin-3-yl)-2-fluorobenzamide (**525**):

A round bottom flask was charged (S)-5-(2-(2-(3,5-difluorophenyl)-1-(2-(4-oxo-3-(trifluoromethyl)-5,6-dihydrocyclopenta[*c*]pyrazol-1(4*H*)-yl)acetamido)ethyl)pyridin-3-yl)-2-fluorobenzamide (10 mg, 0.2 mmol), DCM (3 ml), i-PrOH (0.25 ml), and NaBH₄ (8 mg, 0.2 mmol). The reaction was stirred at room temperature until done by LC/MS then quenched with 1 N HCl and concentrated. The mixture was dissolved in DMF, filtered, and purified by HPLC to obtain the desired compound (7.8 mg, 65%): ¹H NMR (400 MHz, cd₃od) δ 8.69 (d, 1H), 7.60 (d, 1H), 7.47 – 7.38 (m, 2H), 7.28 (s, 1H), 7.22 (d, 1H), 6.66 (s, 1H), 6.33 (s, 2H), 5.35 (s, 1H), 5.07 (s, 1H), 4.80 (s, 2H), 3.06 (t, 2H), 2.83 (d, 2H), 2.56 (s, 2H), 2.41 – 2.30 (m, 1H); MS (*m/z*) 586.4 [*M*+*H*]⁺.

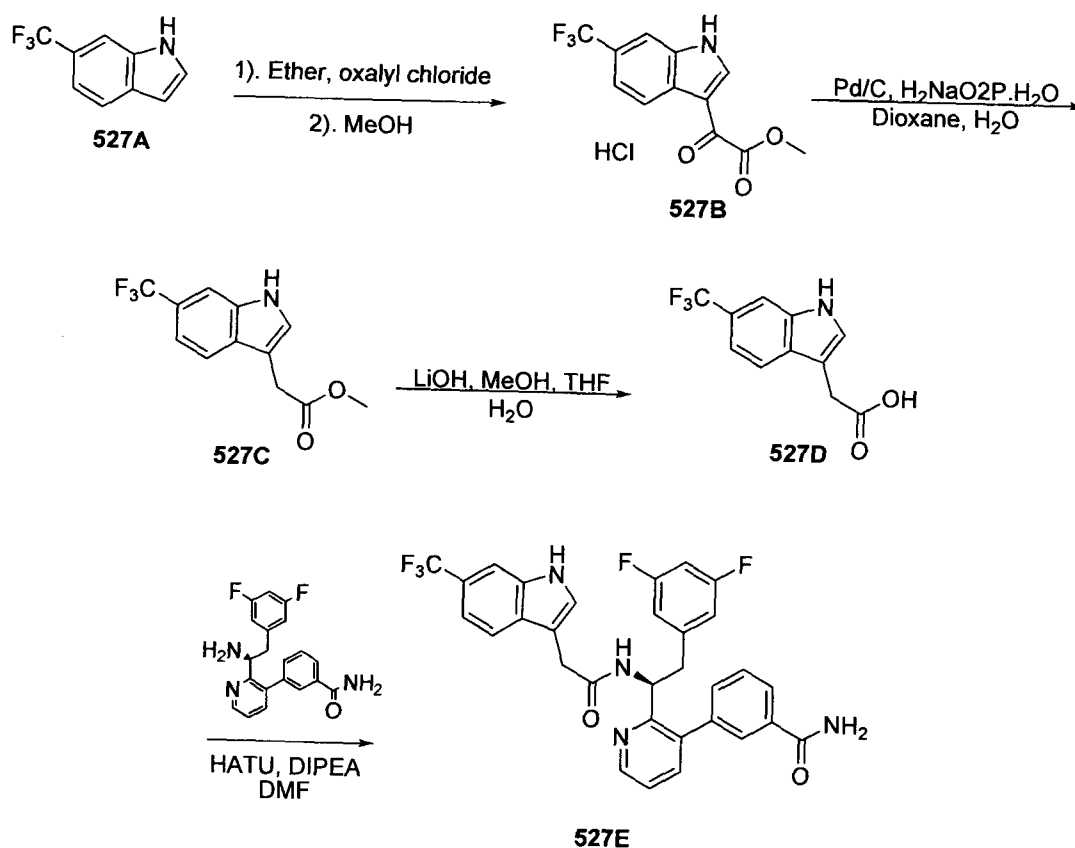
Example 526



Synthesis of (S)-tert-butyl (3-(2-(1-(3-(4-chlorophenyl)pyridin-2-yl)-2-(3,5-difluorophenyl)ethylamino)-2-oxoethyl)-1H-indol-6-yl)methylcarbamate (**526**):

The title compound was prepared according to the method presented in the synthesis of **36F** utilizing **36E** and 2-(6-((tert-butoxycarbonylamino)methyl)-1H-indol-3-yl)acetic acid to provide 24 mg of the desired compound in a 33 % yield: ^1H NMR (400 MHz, dmsO) δ 10.70 (s, 1H), 8.65 – 8.61 (m, 1H), 8.53 (d, 1H), 7.53 (dd, 1H), 7.41 – 7.32 (m, 3H), 7.27 (s, 1H), 7.21 (dd, 3H), 7.13 (s, 1H), 6.98 (s, 1H), 6.92 (t, 1H), 6.76 (d, 1H), 6.42 (d, 2H), 5.19 – 5.08 (m, 1H), 4.12 (d, 2H), 3.44 (d, 2H), 2.95 – 2.88 (m, 2H), 1.36 (s, 9H); MS (m/z) 631.7 [$\text{M}+\text{H}$] $^+$.

Example 527



Synthesis of methyl 2-oxo-2-(6-(trifluoromethyl)-1H-indol-3-yl)acetate hydrochloride (**527B**):
The title compound was prepared according to the method presented in Example **54** substituting 6-(trifluoromethyl)-1H-indole for **54C** to provide the desired compound: MS (m/z) 271.9 [$\text{M}+\text{H}$] $^+$.

Synthesis of methyl 2-(6-(trifluoromethyl)-1H-indol-3-yl)acetate (**527C**):

The title compound was prepared according to the method presented in Example **54** substituting methyl 2-oxo-2-(6-(trifluoromethyl)-1H-indol-3-yl)acetate hydrochloride for **54D** to provide the desired compound: MS (m/z) 257.8 [$\text{M}+\text{H}$] $^+$.

Synthesis of methyl 2-(6-(trifluoromethyl)-1H-indol-3-yl)acetic acid (**527D**):

The title compound was prepared according to the method presented in Example **54** substituting methyl 2-(6-(trifluoromethyl)-1H-indol-3-yl)acetate for **54E** to provide the desired compound:

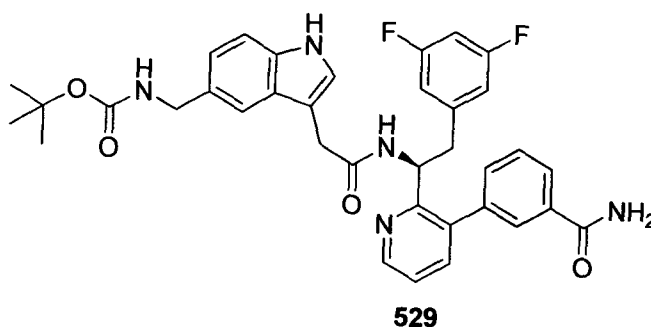
5 MS (m/z) 243.9 $[M+H]^+$.

Synthesis of (S)-3-(2-(2-(3,5-difluorophenyl)-1-(2-(6-(trifluoromethyl)-1H-indol-3-yl)acetamido)ethyl)pyridin-3-yl)benzamide (**527E**):

10 The title compound was prepared according to the method presented in the synthesis of **50D** utilizing **50C** and 2-(6-(trifluoromethyl)-1H-indol-3-yl)acetic acid to provide 27.2 mg of the desired compound in a 55 % yield: ^1H NMR (400 MHz, dmso) δ 11.23 (s, 1H), 8.72 (d, 1H), 8.67 (dd, 1H), 7.96 (s, 1H), 7.87 (d, 1H), 7.75 (s, 1H), 7.64 – 7.57 (m, 2H), 7.53 – 7.37 (m, 4H), 7.26 (d, 1H), 7.11 (d, 1H), 6.87 (t, 1H), 6.49 (d, 2H), 5.17 (dd, 2H), 3.50 (dd, 2H), 2.96 (d, 2H); MS (m/z) 579.2 $[M+H]^+$.

15

Example 529

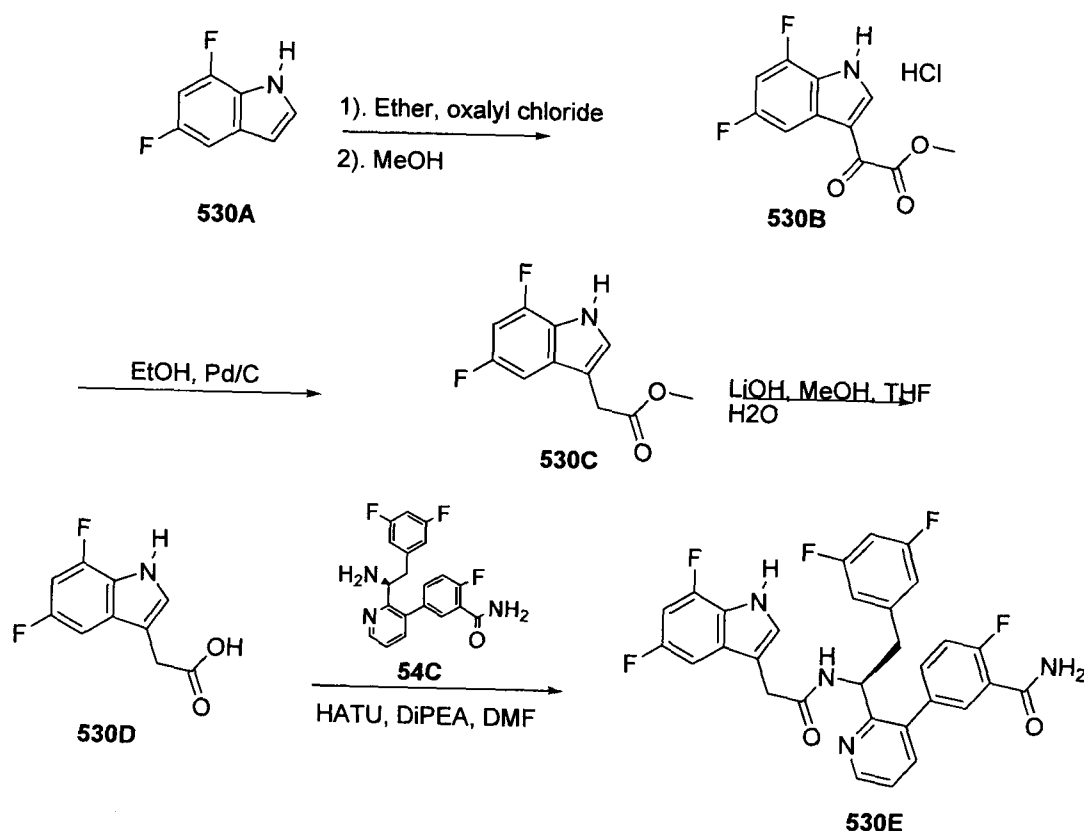


20 Synthesis of (S)-tert-butyl (3-(2-(1-(3-(3-carbamoylphenyl)pyridin-2-yl)-2-(3,5-difluorophenyl)ethylamino)-2-oxoethyl)-1H-indol-5-yl)methylcarbamate (**529**):

The title compound was prepared according to the method presented in the synthesis of **50D** utilizing **50C** and **491E** to provide 20 mg of the desired compound in a 27 % yield: ^1H NMR (400 MHz, dmso) δ 10.71 (s, 1H), 8.64 (d, 1H), 8.52 (d, 1H), 7.93 (s, 1H), 7.86 (d, 1H), 7.71 (s, 1H), 7.59 (d, 1H), 7.47 – 7.33 (m, 4H), 7.27 – 7.14 (m, 3H), 7.00 – 6.91 (m, 2H), 6.86 (t, 1H), 6.41 (d, 2H), 5.22 (d, 1H), 4.10 (d, 2H), 3.45 (s, 2H), 2.94 (d, 2H), 1.34 (s, 9H); MS (m/z) 640.0 $[M+H]^+$.

25

Example 530



Synthesis of methyl 2-(5,7-difluoro-1H-indol-3-yl)-2-oxoacetate hydrochloride (**530B**):

The title compound was prepared according to the method presented in Example **54** substituting 5,7-difluoro-1H-indole for **54C** to provide the desired compound: MS (*m/z*) 240.1 [M+H]⁺.

5

Synthesis of methyl 2-(5,7-difluoro-1H-indol-3-yl)acetate (**530C**):

A flask is charged with methyl 2-(5,7-difluoro-1H-indol-3-yl)-2-oxoacetate hydrochloride (750 mg, 2.7 mmol), EtOH (150 ml), EtOAc (49 ml), and AcOH (1 ml). The mixture was passed through a flow hydrogenator fitted with a 10% Pd/C cartridge (0.8 ml/min, 40 bar, 100 °C). The mixture was collected into a flask charged with NaHCO₃. Once complete, the mixture is filtered and concentrated. The mixture was dissolved in DCM and remaining starting material is precipitated out by the addition of hexane. The organic layer is then concentrated to give the desired compound (150 mg, 25%): MS (*m/z*) 226.1 [M+H]⁺.

10

Synthesis of 2-(5,7-difluoro-1H-indol-3-yl)acetic acid (**530D**):

The title compound was prepared according to the method presented in Example **54** substituting methyl 2-(5,7-difluoro-1H-indol-3-yl)acetate for **54E** to provide the desired compound: MS (*m/z*) 212.1 [M+H]⁺.

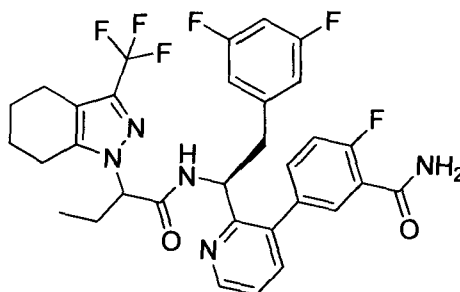
15

Synthesis of (S)-5-(2-(1-(2-(5,7-difluoro-1H-indol-3-yl)acetamido)-2-(3,5-difluorophenyl)ethyl)pyridin-3-yl)-2-fluorobenzamide (**530E**):

The title compound was prepared according to the method presented in the synthesis of **54G** substituting 2-(5,7-difluoro-1H-indol-3-yl)acetic acid for **54F** to provide the desired compound
5 (33 mg, 41%): ^1H NMR (400 MHz, dmsO) δ 11.37 (s, 1H), 8.73 – 8.60 (m, 2H), 7.64 (d, 2H), 7.57 (dd, 1H), 7.48 (d, 1H), 7.38 (dd, 2H), 7.33 – 7.21 (m, 1H), 7.14 (d, 1H), 6.98 (dd, 1H), 6.84 (t, 2H), 6.50 (d, 2H), 5.13 (dd, 1H), 3.51 – 3.35 (m, 2H), 2.96 (d, 2H); MS (m/z) 565.6 $[\text{M}+\text{H}]^+$.

Example 531

10



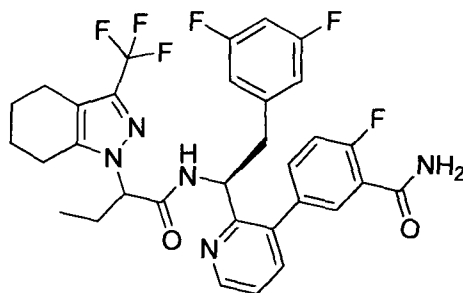
531

Synthesis of 5-(2-((1S)-2-(3,5-difluorophenyl)-1-(2-(3-(trifluoromethyl)-4,5,6,7-tetrahydro-1H-indazol-1-yl)butanamido)ethyl)pyridin-3-yl)-2-fluorobenzamide (**531**):

The title compound was separated from the diastereomeric mixture of **504E** by semi-preparative
15 chiral HPLC fitted with a Chiralcel AZ-H column running a 70:30 mixture of Hep:IPA to obtain the desired compound (RT 7.8 minutes, 4.9 mg): ^1H NMR (400 MHz, dmsO) δ 8.87 (d, 1H), 8.64 (d, 1H), 7.69 (s, 2H), 7.64 (d, 1H), 7.56 (d, 1H), 7.49 (s, 1H), 7.43 – 7.32 (m, 2H), 6.96 (s, 1H), 6.65 (d, 2H), 5.08 (d, 1H), 4.66 (s, 1H), 3.00 (d, 2H), 2.39 (s, 2H), 1.94 (s, 3H), 1.57 (s, 3H), 1.53 – 1.42 (m, 2H), 0.68 (t, 3H); MS (m/z) 630.9 $[\text{M}+\text{H}]^+$.

20

Example 532

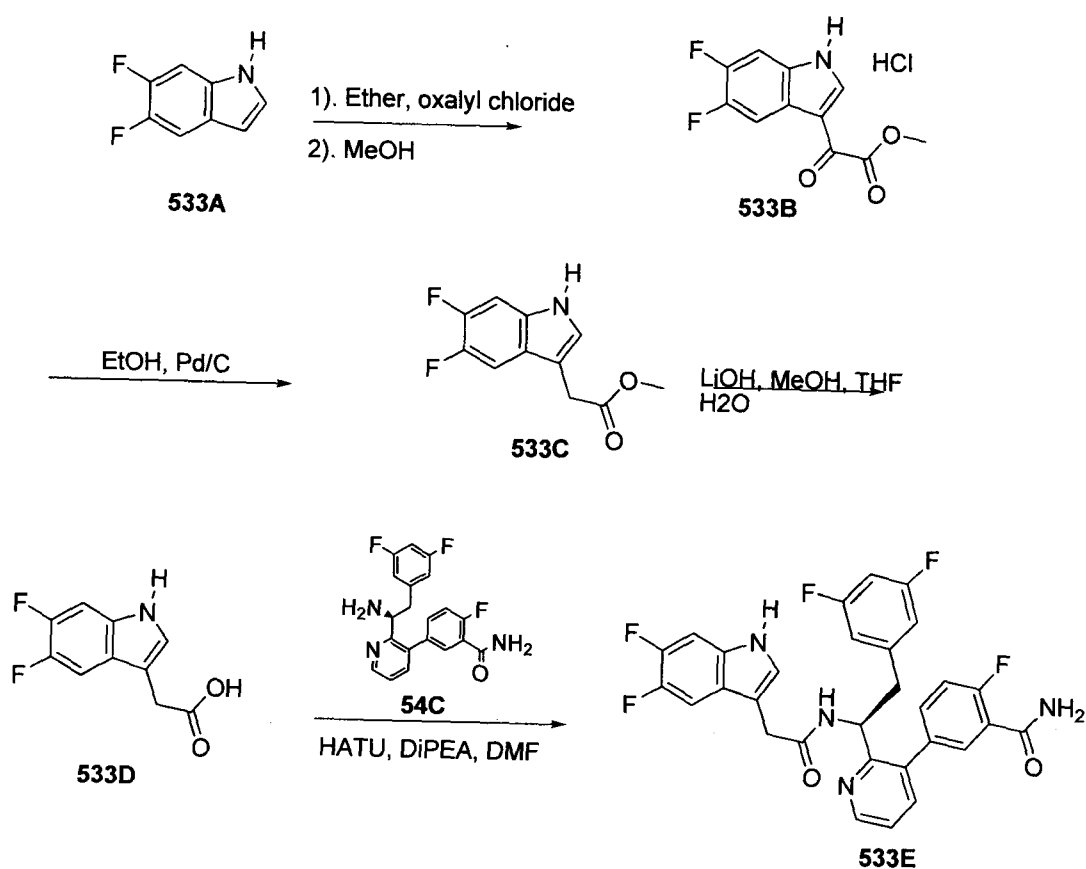


532

Synthesis of 5-(2-((1S)-2-(3,5-difluorophenyl)-1-(2-(3-(trifluoromethyl)-4,5,6,7-tetrahydro-1H-indazol-1-yl)butanamido)ethyl)pyridin-3-yl)-2-fluorobenzamide (**532**):

The title compound was separated from the diastereomeric mixture of **504E** by semi-preparative chiral HPLC fitted with a Chiralcel AZ-H column running a 70:30 mixture of Hep:IPA to obtain the desired compound (RT 10.1 minutes, 4.9 mg): ^1H NMR (400 MHz, $\text{dms-}d_6$) δ 8.77 (d, 1H), 8.61 (d, 1H), 7.66 (s, 2H), 7.61 (d, 1H), 7.54 (s, 1H), 7.50 – 7.43 (m, 1H), 7.41 – 7.37 (m, 1H), 7.37 – 7.29 (m, 1H), 6.94 (s, 1H), 6.56 (d, 2H), 5.12 (s, 1H), 4.71 (s, 1H), 2.96 (d, 2H), 2.62 – 2.44 (m, 2H), 2.41 (s, 2H), 2.29 (s, 2H), 1.91 (s, 2H), 1.60 (s, 3H), 0.63 (t, 3H); MS (m/z) 630.9 $[\text{M}+\text{H}]^+$.

Example 533



Synthesis of methyl 2-(5,6-difluoro-1H-indol-3-yl)-2-oxoacetate hydrochloride (**533B**):

The title compound was prepared according to the method presented in Example 54 substituting 5,6-difluoro-1H-indole for **54C** to provide the desired compound: MS (m/z) 240.1 $[\text{M}+\text{H}]^+$.

Synthesis of methyl 2-(5,6-difluoro-1H-indol-3-yl)acetate (**533C**):

The title compound was prepared according to the method presented in Example 530 substituting methyl 2-(5,6-difluoro-1H-indol-3-yl)-2-oxoacetate hydrochloride for **530B** to provide the desired compound: MS (m/z) 226.0 $[M+H]^+$.

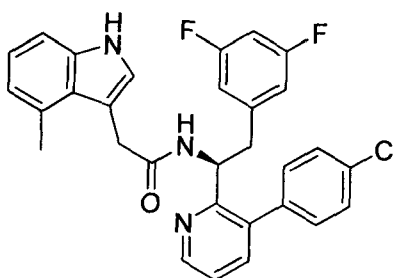
5 Synthesis of 2-(5,6-difluoro-1H-indol-3-yl)acetic acid (**533D**):

The title compound was prepared according to the method presented in Example 54 substituting methyl 2-(5,6-difluoro-1H-indol-3-yl)acetate for **54E** to provide the desired compound: MS (m/z) 212.1 $[M+H]^+$.

10 Synthesis of (S)-5-(2-(1-(2-(5,6-difluoro-1H-indol-3-yl)acetamido)-2-(3,5-difluorophenyl)ethyl)pyridin-3-yl)-2-fluorobenzamide (**533E**):

The title compound was prepared according to the method presented in the synthesis of **54G** substituting 2-(5,6-difluoro-1H-indol-3-yl)acetic acid for **54F** to provide the desired compound (35 mg, 44%): ^1H NMR (400 MHz, dmso) δ 10.92 (s, 1H), 8.71 – 8.62 (m, 2H), 7.64 (d, 2H), 7.60 – 7.56 (m, 1H), 7.48 (dd, 1H), 7.38 (dd, 2H), 7.35 – 7.19 (m, 3H), 7.08 (d, 1H), 6.85 (t, 1H), 6.50 (d, 2H), 5.13 (dd, 1H), 3.49 – 3.34 (m, 2H), 3.02 – 2.91 (m, 2H); MS (m/z) 565.8 $[M+H]^+$.

Example 534



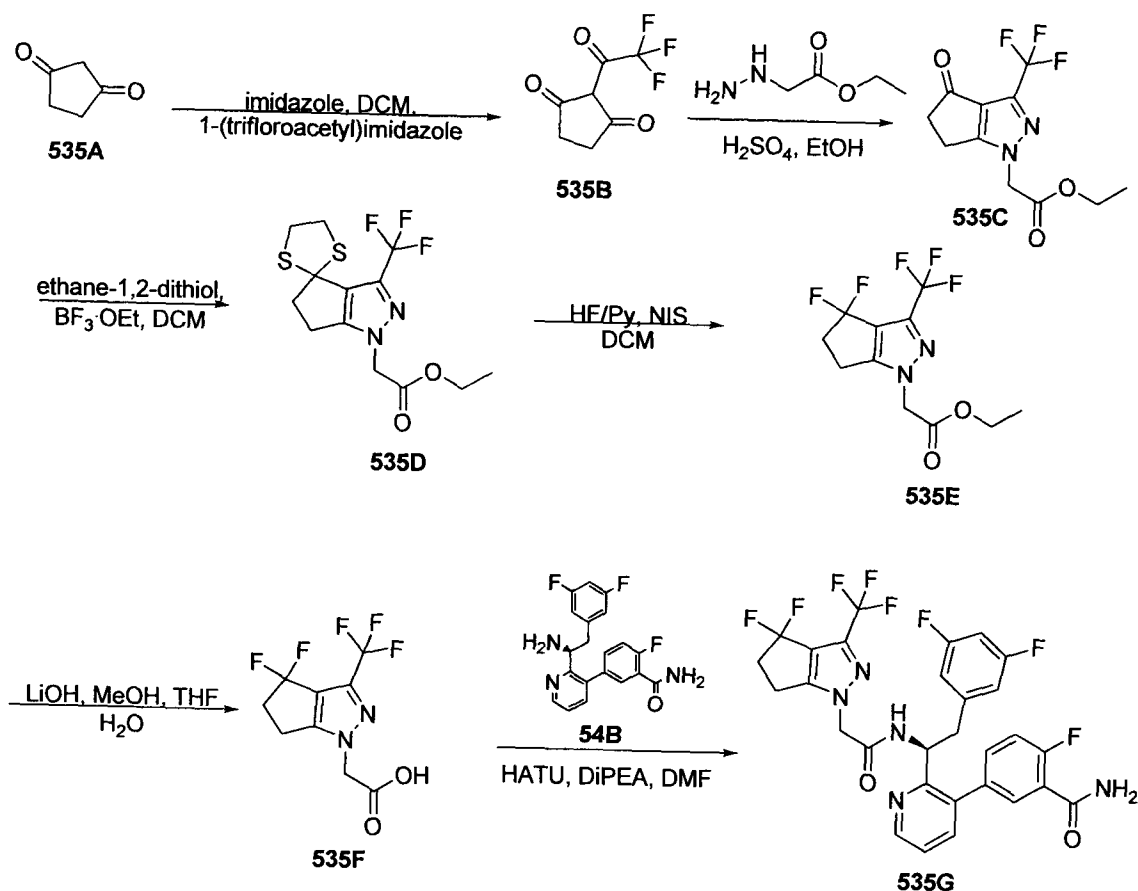
534

20 Synthesis of (S)-N-(1-(3-(4-chlorophenyl)pyridin-2-yl)-2-(3,5-difluorophenyl)ethyl)-2-(4-methyl-1H-indol-3-yl)acetamide (**534**):

The title compound was prepared according to the method presented in the synthesis of **36F** utilizing **36E** and 2-(4-methyl-1H-indol-3-yl)acetic acid to provide 17 mg of the desired

25 compound in a 28 % yield: ^1H NMR (400 MHz, dmso) δ 10.74 (s, 1H), 8.59 (dd, 1H), 8.30 (d, 1H), 7.54 (dd, 1H), 7.41 (d, 2H), 7.36 (dd, 1H), 7.21 (d, 2H), 7.09 (d, 1H), 6.95 (dd, 2H), 6.88 – 6.81 (m, 1H), 6.57 (d, 1H), 6.41 (d, 2H), 5.17 (dd, 1H), 3.69 – 3.56 (m, 2H), 2.92 (dd, 2H), 2.30 (s, 3H); MS (m/z) 516.8 $[M+H]^+$.

Example 535



5 Synthesis of 2-(2,2,2-trifluoroacetyl)cyclopentane-1,3-dione (**535B**):

A round bottom is charged with cyclopentane-1,3-dione (2 g, 20 mmol), imidazole (1.4 g, 20 mmol), DCM (60 ml), and 1-(trifluoroacetyl)imidazole (3.35 g, 20 mmol). The resulting mixture was stirred for 3 hours and quenched with 1 M HCl. The resulting mixture was extracted 2X DCM. The organic layer was dried over sodium sulfate, filtered, concentrated and used with no further purification to give the desired compound (2.8 g, 70%): MS (*m/z*) 195.0 [M+H]⁺.

Synthesis of ethyl 2-(4-oxo-3-(trifluoromethyl)-5,6-dihydrocyclopenta[c]pyrazol-1(4H)-yl)acetate (**535C**):

A round bottom is charged with 2-(2,2,2-trifluoroacetyl)cyclopentane-1,3-dione (2.8 g, 14 mmol), ethyl 2-hydrazinylacetate (1.9 g, 12 mmol), H₂SO₄ (0.3 ml), and EtOH (15 ml). The resulting mixture was stirred at reflux overnight. The mixture was concentrated and diluted with EtOAc and aq. NaHCO₃. The organic layer was dried over sodium sulfate, filtered, concentrated

and purified by flash chromatography to give the desired compound (2.6 g, 67%): MS (m/z) 277.1 $[M+H]^+$.

5 Synthesis of ethyl 2-(3-(trifluoromethyl)-5,6-dihydro-1H-spiro[cyclopenta[c]pyrazole-4,2'-[1,3]dithiolane]-1-yl)acetate (**535D**):

A round bottom is charged with ethyl 2-(4-oxo-3-(trifluoromethyl)-5,6-dihydrocyclopenta[c]pyrazol-1(4H)-yl)acetate (300 mg, 1 mmol), DCM (2 ml), ethane-1,2-dithiol (0.1 ml, 1.2 mmol), Boron trifluoride etherate (0.13 ml, 1.1 mmol), and AcOH (1 ml). The resulting mixture was stirred overnight. The mixture was diluted with H₂O and extracted 2X
10 DCM. The organic layers were dried over sodium sulfate, filtered, concentrated and was used without further purification to give the desired compound (320 mg, 91%): MS (m/z) 353.3 $[M+H]^+$.

15 Synthesis of ethyl 2-(4,4-difluoro-3-(trifluoromethyl)-5,6-dihydrocyclopenta[c]pyrazol-1(4H)-yl)acetate (**535E**):

A round bottom is charged with ethyl 2-(3-(trifluoromethyl)-5,6-dihydro-1H-spiro[cyclopenta[c]pyrazole-4,2'-[1,3]dithiolane]-1-yl)acetate (100 mg, 0.3 mmol), DCM (1 ml), and HF/Py (1 ml). The resulting mixture was cooled to -45 °C and then a mixture of NIS (158 mg, 0.7 mmol) and DCM (1 ml) was added to the reaction. The mixture was stirred allowing to
20 slowly warm to -30 °C over 3 hours. The reaction was quenched with aq. NaHCO₃ and extracted with DCM. The organic layer was washed with water, dried over sodium sulfate, filtered, concentrated and purified by flash chromatography to give the desired compound (35 mg, 42%): MS (m/z) 299.1 $[M+H]^+$.

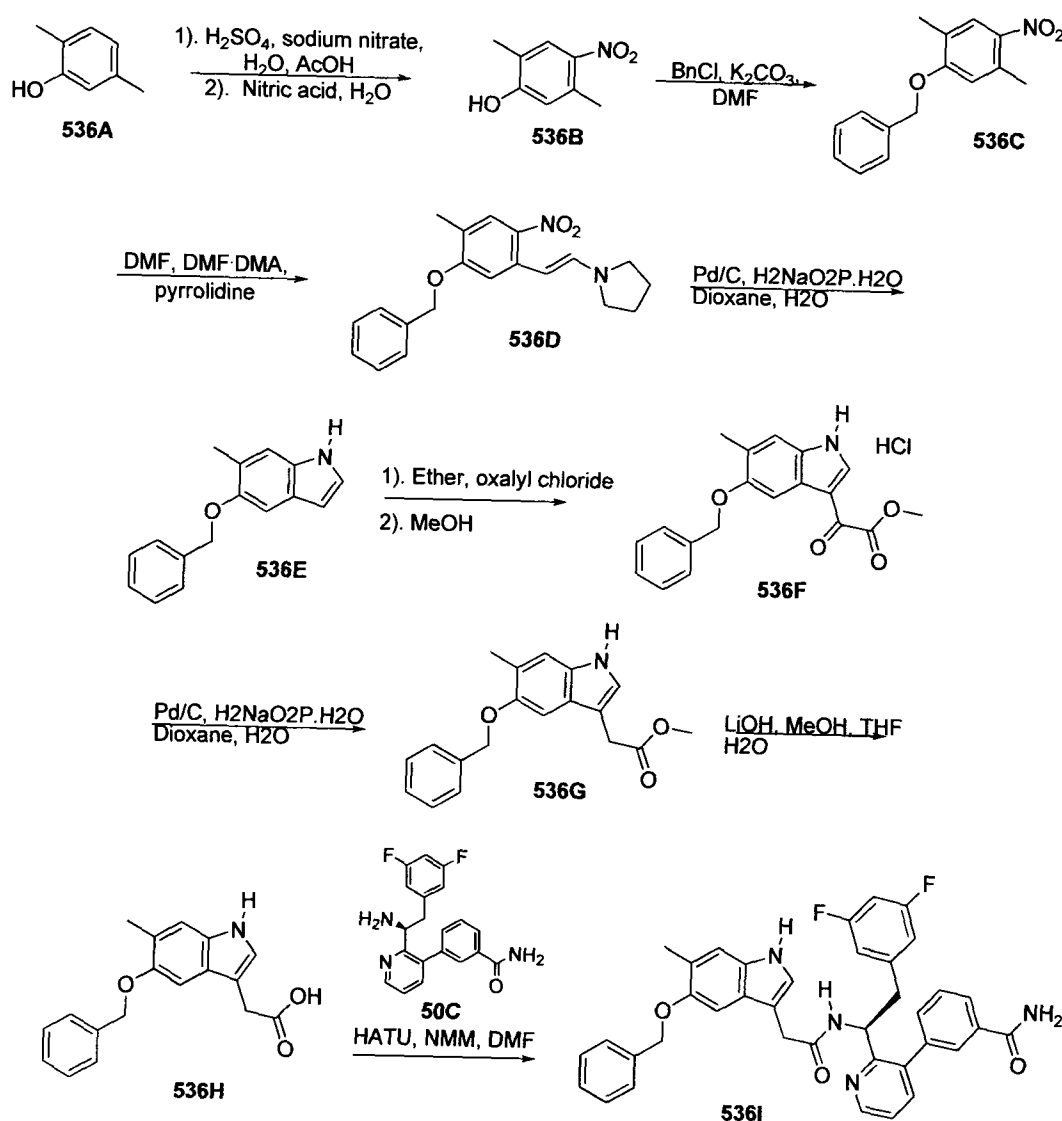
25 Synthesis of 2-(4,4-difluoro-3-(trifluoromethyl)-5,6-dihydrocyclopenta[c]pyrazol-1(4H)-yl)acetic acid (**535F**):

The title compound was prepared according to the method presented in Example 491 substituting ethyl 2-(4,4-difluoro-3-(trifluoromethyl)-5,6-dihydrocyclopenta[c]pyrazol-1(4H)-yl)acetate for **491D** to provide the desired compound: MS (m/z) 271.0 $[M+H]^+$.
30

Synthesis of (S)-5-(2-(1-(2-(4,4-difluoro-3-(trifluoromethyl)-5,6-dihydrocyclopenta[c]pyrazol-1(4H)-yl)acetamido)-2-(3,5-difluorophenyl)ethyl)pyridin-3-yl)-2-fluorobenzamide (**535G**):

The title compound was prepared according to the method presented in the synthesis of **54G** utilizing **54B** and 2-(4,4-difluoro-3-(trifluoromethyl)-5,6-dihydrocyclopenta[c]pyrazol-1(4H)-yl)acetic acid to provide 20 mg of the desired compound in a 24% yield: ^1H NMR (400 MHz, cd_3od) δ 8.69 (d, 1H), 7.58 (d, 1H), 7.43 (s, 1H), 7.39 (dd, 1H), 7.33 – 7.26 (m, 1H), 7.25 – 7.17 (m, 1H), 6.65 (s, 1H), 6.32 (d, 2H), 5.39 – 5.31 (m, 1H), 4.87 (s, 2H), 3.05 (ddd, 5H), 2.87 (s, 2H); MS (m/z) 624.2 $[\text{M}+\text{H}]^+$.

Example 536



10 Synthesis of 2,5-dimethyl-4-nitrophenol (**536B**):

A round bottom was charged with 2,5-dimethylphenol (2 g, 16.4 mmol), H_2SO_4 (0.7 ml), AcOH (5 ml), and cool the reaction to 0 °C. To the cooled stirring reaction slowly add sodium nitrate (1.15 g, 14 mmol) dissolved in H_2O (3.3 ml) keeping the temperature between 8-10 °C. After 10 minutes add ice and filter off solid. The solid was air dried for 30 minutes after which it was

slowly added to a RB with a solution of 70% nitric acid (1.65 ml) and H₂O (5 ml) heated to 50 °C. The reaction was allowed to stir overnight. Water was added and the solution was filtered. The cake was rinsed with water then dissolved in EtOAc, dried over sodium sulfate, filtered, concentrated. The mixture was dissolved in DCM followed by hexane to precipitate out solid, filtered, and dried under vacuum to give the desired compound (1.5 g, 56%): ¹H NMR (400 MHz, cdcl₃) δ 7.92 (s, 1H), 7.24 (s, 1H), 6.65 (s, 1H), 5.26 (s, 1H), 2.55 (s, 3H), 2.25 (s, 3H).

Synthesis of 1-(benzyloxy)-2,5-dimethyl-4-nitrobenzene (**536C**):

A round bottom was charged with 2,5-dimethyl-4-nitrophenol (1.5 g, 9 mmol), DMF(11 ml), K₂CO₃ (1.3g, 9.1 mmol), and BnCl (1.5 ml, 12 mmol). The mixture was stirred at RT for 2 hours. The reaction was diluted with H₂O and extracted 2X with EtOAc. The organic layer was dried over sodium sulfate, filtered, concentrated and purified by flash chromatography to give the desired compound (1.5 mg, 65 %): MS (*m/z*) 258.0 [M+H]⁺.

Synthesis of 1-(5-(benzyloxy)-4-methyl-2-nitrostyryl)pyrrolidine (**536D**):

A round bottom was charged with 1-(benzyloxy)-2,5-dimethyl-4-nitrobenzene (1.5 g, 5.8 mmol), DMF(5 ml), DMFDMA (1.2 ml, 9 mmol) and pyrrolidine (0.73 ml, 9 mmol). The resulting mixture was heated to 110 °C for 3 hours. The mixture was concentrated to 1/3 volume then diluted with DCM then the desired compound was precipitated by the addition of hexane. The solid was filtered and dried under vacuum to give the desired compound (1.4 g, 71%).

Synthesis of methyl 5-(benzyloxy)-6-methyl-1H-indole (**536E**):

A round bottom was charged with 1-(5-(benzyloxy)-4-methyl-2-nitrostyryl)pyrrolidine (1.1 g, 3.4 mmol), dioxane (38 ml), Pd/C (400 mg), H₂NaO₂P•H₂O (800 mg, 7.5 mmol), and H₂O (3.8 ml). The resulting mixture was stirred at 65 °C until done as indicated by LC/MS. The reaction mixture was cooled to RT and filtered over a plug of celite, rinsing with ethyl acetate. The layers were partitioned and the organic layer was dried over sodium sulfate, filtered, concentrated and purified by flash chromatography to give the desired compound as a white solid (540 mg, 67%): MS (*m/z*) 238.0 [M+H]⁺.

Synthesis of methyl 2-(5-(benzyloxy)-6-methyl-1H-indol-3-yl)-2-oxoacetate hydrochloride (**536F**):

The title compound was prepared according to the method presented in Example 54 substituting 5-(benzyloxy)-6-methyl-1H-indole for 54C to provide the desired compound: MS (m/z) 323.9 $[M+H]^+$.

5 Synthesis of methyl 2-(5-(benzyloxy)-6-methyl-1H-indol-3-yl)acetate (**536G**):

The title compound was prepared according to the method presented in Example 54 substituting methyl 2-(5-(benzyloxy)-6-methyl-1H-indol-3-yl)-2-oxoacetate hydrochloride for 54D to provide the desired compound: MS (m/z) 310.1 $[M+H]^+$.

10 Synthesis of 2-(5-(benzyloxy)-6-methyl-1H-indol-3-yl)acetic acid (**536H**):

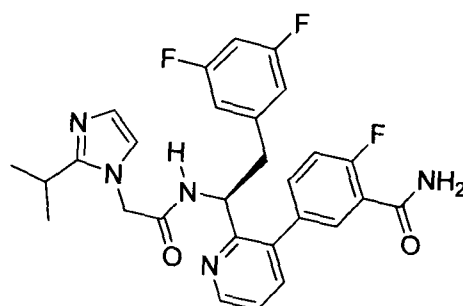
The title compound was prepared according to the method presented in Example 54 substituting methyl 2-(5-(benzyloxy)-6-methyl-1H-indol-3-yl)acetate for 54E to provide the desired compound: MS (m/z) 296.0 $[M+H]^+$.

15 Synthesis of (S)-3-(2-(1-(2-(5-(benzyloxy)-6-methyl-1H-indol-3-yl)acetamido)-2-(3,5-difluorophenyl)ethyl)pyridin-3-yl)benzamide (**536I**):

The title compound was prepared according to the method presented in the synthesis of 50D utilizing 50C and 2-(5-(benzyloxy)-6-methyl-1H-indol-3-yl)acetic acid to provide 35 mg of the desired compound in a 40 % yield: ^1H NMR (400 MHz, dmso) δ 10.51 (s, 1H), 8.59 (d, 1H),

20 8.47 (d, 1H), 7.94 (s, 1H), 7.86 (d, 1H), 7.71 (s, 1H), 7.58 (d, 1H), 7.43 (t, 3H), 7.40 – 7.33 (m, 5H), 7.29 (d, 1H), 7.05 (d, 2H), 6.89 (s, 1H), 6.83 (t, 1H), 6.39 (d, 2H), 5.23 (d, 1H), 4.93 (s, 2H), 3.44 (s, 2H), 2.92 (d, 2H), 2.22 (s, 3H); MS (m/z) 631.4 $[M+H]^+$.

Example 537

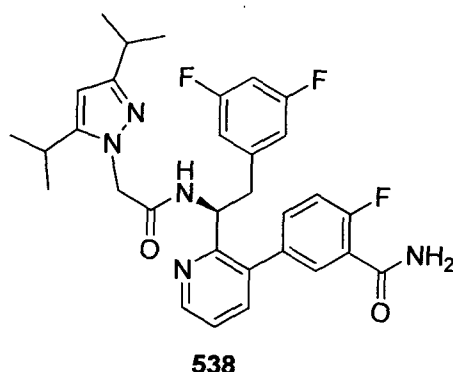


537

25 Synthesis of (S)-5-(2-(2-(3,5-difluorophenyl)-1-(2-(2-isopropyl-1H-imidazol-1-yl)acetamido)ethyl)pyridin-3-yl)-2-fluorobenzamide (**537**):

The title compound was prepared according to the method presented in Example 56 substituting 2-isopropyl-1H-imidazole for 1H-benzo[g]indole to provide the desired compound (14 mg, 38%): ^1H NMR (400 MHz, dmsO) δ 9.16 (d, 1H), 8.70 (d, 1H), 7.65 (dd, 3H), 7.53 (d, 2H), 7.43 (dd, , 1H), 7.38 (d, 2H), 7.37 – 7.28 (m, 1H), 6.97 (t, 1H), 6.64 (d, 2H), 5.16 (d, 1H), 4.87 (q, 2H), 3.04 (dt, 2H), 2.86 – 2.74 (m, 1H), 1.07 (dd, 6H); MS (m/z) 522.7 $[\text{M}+\text{H}]^+$.

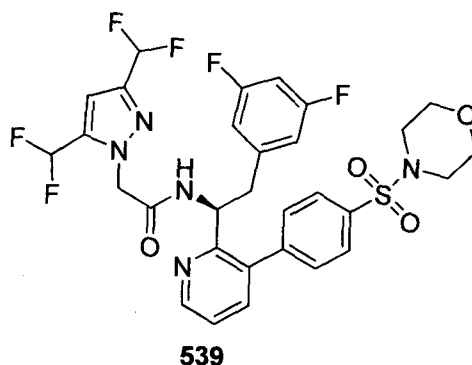
Example 538



Synthesis of (S)-5-(2-(2-(3,5-difluorophenyl)-1-(2-(3,5-diisopropyl-1H-pyrazol-1-yl)acetamido)ethyl)pyridin-3-yl)-2-fluorobenzamide (**538**):

The title compound was prepared according to the method presented in the synthesis of **56B** substituting 3,5-diisopropyl-1H-pyrazole for 1H-benzo[g]indole to provide the desired compound (8 mg, 20 %): ^1H NMR (400 MHz, dmsO) δ 8.63 (d, 1H), 8.47 (d, 1H), 7.63 (dd, 3H), 7.48 (d, 1H), 7.40 (dd, 2H), 7.36 – 7.26 (m, 1H), 6.92 (s, 1H), 6.53 (d, 2H), 5.82 (s, 1H), 5.17 (d, 1H), 4.57 (s, 2H), 2.96 (dd, 2H), 2.77 – 2.68 (m, 1H), 2.67 – 2.53 (m, 1H), 1.10 (d, 6H), 0.98 (d, 6H); MS (m/z) 564.4 $[\text{M}+\text{H}]^+$.

Example 539

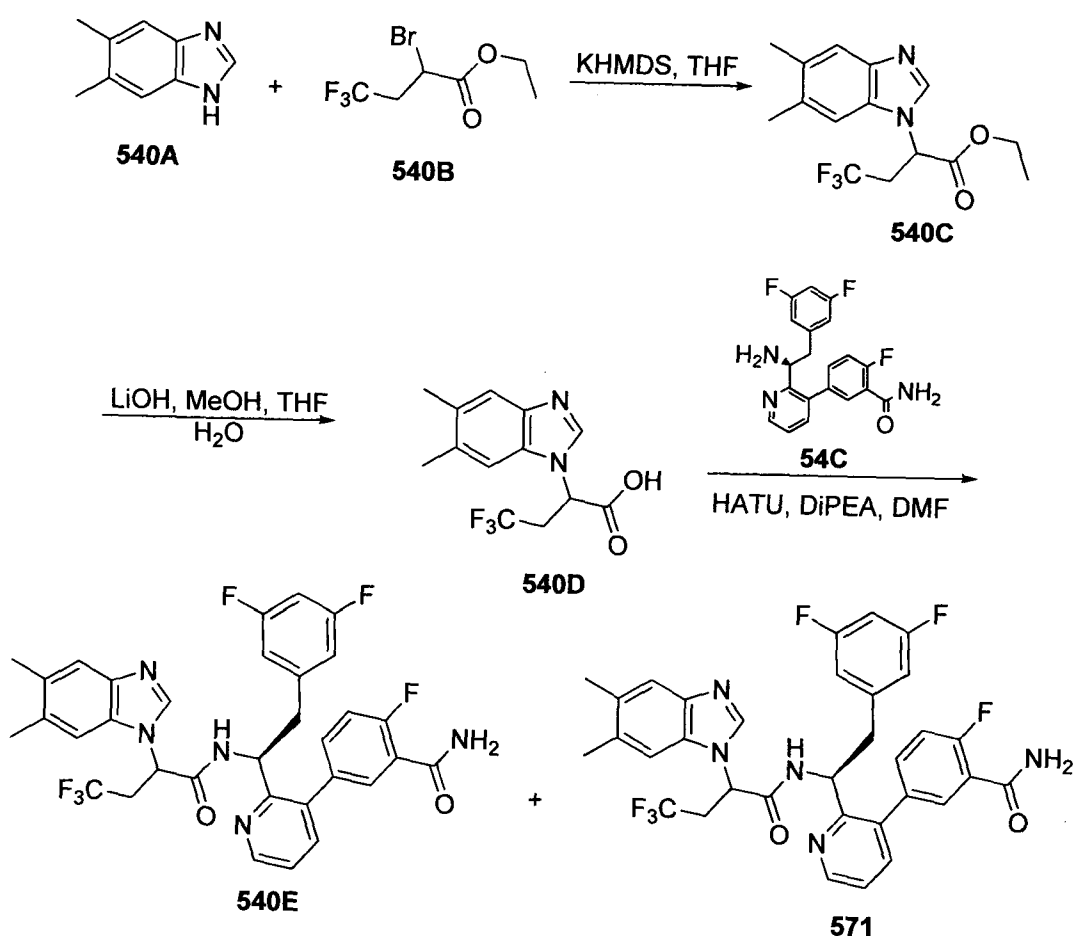


Synthesis of (S)-2-(3,5-bis(difluoromethyl)-1H-pyrazol-1-yl)-N-(2-(3,5-difluorophenyl)-1-(3-(4-(morpholinosulfonyl)phenyl)pyridin-2-yl)ethyl)acetamide (**539**):

The title compound was prepared according to the method presented in the synthesis of **512C** substituting 4-(morpholinosulfonyl)phenylboronic acid for 5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrrolo[2,3-b]pyridine to provide the desired compound (21 mg, 17 %):

¹H NMR (400 MHz, dmso) δ 9.09 (d, 1H), 8.72 (dd, 1H), 7.70 (d, 2H), 7.61 (dd, 1H), 7.49 – 7.35 (m, 3H), 7.15 (d, 1H), 7.08 – 6.80 (m, 4H), 6.34 (d, 2H), 5.14 (dd, 1H), 4.99 (s, 2H), 3.66 – 3.57 (m, 4H), 2.95 (d, 2H), 2.88 (d, 4H); MS (*m/z*) 668.2 [M+H]⁺.

Examples 540 and 571



Synthesis of ethyl 2-(5,6-dimethyl-1H-benzodimidazol-1-yl)-4,4,4-trifluorobutanoate (**540C**):

The title compound was prepared according to the method presented in Example **478**

substituting **540A** for **478A** and **540B** for **478B** to provide the desired compound: MS (*m/z*) 315.5 [M+H]⁺.

Synthesis of 2-(5,6-dimethyl-1H-benzodimidazol-1-yl)-4,4,4-trifluorobutanoic acid (**540D**):

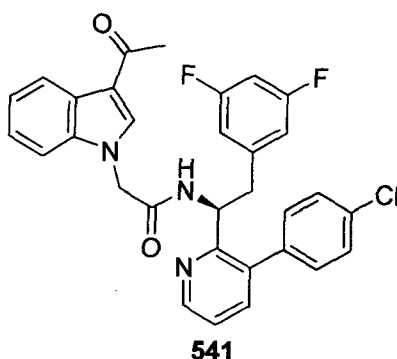
The title compound was prepared according to the method presented in Example 478 ethyl 2-(5,6-dimethyl-1H-benzo[d]imidazol-1-yl)-4,4,4-trifluorobutanoate for 478C to provide the desired compound: MS (m/z) 287.3 $[M+H]^+$.

- 5 Synthesis of 5-(2-((1S)-2-(3,5-difluorophenyl)-1-(2-(5,6-dimethyl-1H-benzo[d]imidazol-1-yl)-4,4,4-trifluorobutanamido)ethyl)pyridin-3-yl)-2-fluorobenzamide (540E and 571):

The title compound was prepared according to the method presented in the synthesis of 54G substituting 2-(5,6-dimethyl-1H-benzo[d]imidazol-1-yl)-4,4,4-trifluorobutanoic acid for 2-(5-(trifluoromethyl)-1H-indol-3-yl)acetic acid to provide the desired compounds (540E, the first
10 peak off HPLC, 7 mg, 8%; 571, the second peak off HPLC, 12 mg, 14%): 540E ^1H NMR (400 MHz, dmso) δ 8.80 (d, 1H), 8.66 (d, 1H), 8.59 – 8.50 (m, 1H), 7.62 (s, 2H), 7.55 (d, 1H), 7.51 (s, 1H), 7.42 (s, 1H), 7.39 (d, 1H), 7.31 (s, 1H), 7.21 (d, 2H), 6.75 (s, 1H), 6.28 (d, 2H), 5.83 – 5.73 (m, 1H), 5.03 (d, 1H), 3.42 – 3.31 (m, 2H), 3.12 (s, 2H), 2.31 (s, 3H), 2.28 (s, 3H); MS (m/z) 640.4 $[M+H]^+$; 571 MS (m/z) 640.4 $[M+H]^+$.

15

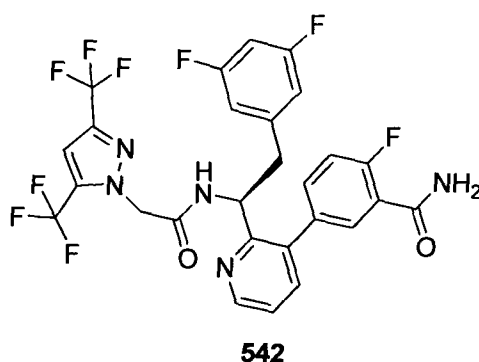
Example 541



- 20 Synthesis of (S)-2-(3-acetyl-1H-indol-1-yl)-N-(1-(3-(4-chlorophenyl)pyridin-2-yl)-2-(3,5-difluorophenyl)ethyl)acetamide (541):

The title compound was prepared according to the method presented in the synthesis of 36F utilizing 36E and 2-(3-acetyl-1H-indol-1-yl)acetic acid to provide 16.2 mg of the desired
25 compound in a 25% yield: ^1H NMR (400 MHz, dmso) δ 9.13 (d, 1H), 8.71 (dd, 1H), 8.14 (s, 1H), 8.10 (d, 1H), 7.57 (dd, 1H), 7.40 (dd, 3H), 7.21 (d, 2H), 7.17 – 7.05 (m, 3H), 6.99 (t, 1H), 6.50 (d, 2H), 5.21 – 5.10 (m, 1H), 4.88 (s, 2H), 2.99 (d, 2H), 2.36 (s, 3H); MS (m/z) 544.7 $[M+H]^+$.

Example 542

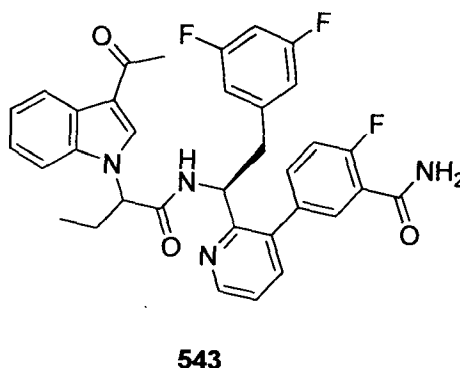


Synthesis of (S)-5-(2-(1-(2-(3,5-bis(trifluoromethyl)-1H-pyrazol-1-yl)acetamido)-2-(3,5-difluorophenyl)ethyl)pyridin-3-yl)-2-fluorobenzamide (**542**):

- 5 The title compound was prepared according to the method presented in Example 56 substituting 3,5-bis(trifluoromethyl)-1H-pyrazole for 1H-benzo[g]indole and heating to 95 °C to provide the desired compound (4 mg, 10%): ¹H NMR (400 MHz, dmso) δ 9.05 (d, 1H), 8.68 (d, 1H), 7.63 (dd, 3H), 7.47 (d, 2H), 7.45 – 7.41 (m, 1H), 7.40 (s, 1H), 7.35 – 7.27 (m, 1H), 6.91 (t, 1H), 6.57 (d, 2H), 5.14 (d, 1H), 5.09 – 4.95 (m, 2H), 3.08 – 2.90 (m, 2H); MS (*m/z*) 616.5 [M+H]⁺.

10

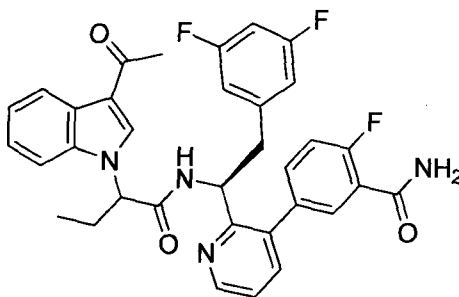
Example 543



Synthesis of 5-(2-((1S)-1-(2-(3-acetyl-1H-indol-1-yl)butanamido)-2-(3,5-difluorophenyl)ethyl)pyridin-3-yl)-2-fluorobenzamide (**543**):

- 15 The title compound was separated from the diastereomeric mixture of **554** by semi-preparative chiral HPLC fitted with a Chiralpak IA column running a 70:30 mixture of Hep:IPA to obtain the desired compound (RT 6.4 minutes, 11 mg): ¹H NMR (400 MHz, dmso) δ 9.21 (d, 1H), 8.61 (d, 1H), 8.23 (s, 1H), 8.10 (d, 1H), 7.66 (d, 2H), 7.51 (dd, 3H), 7.33 (dd, 2H), 7.16 (dt, 3H), 6.97 (s, 1H), 6.65 (d, 2H), 5.14 (d, 1H), 5.04 (t, 1H), 3.04 (d, 2H), 2.37 (s, 3H), 2.04 – 1.89 (m, 2H),
20 0.65 (t, 3H); MS (*m/z*) 599.6 [M+H]⁺.

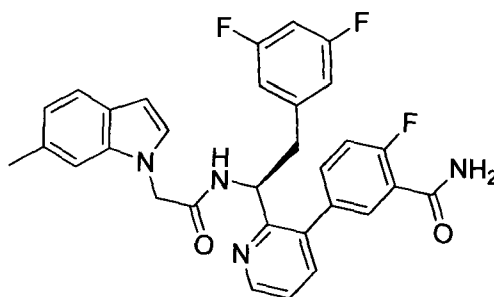
Example 544

**544**

Synthesis of 5-(2-((1S)-1-(2-(3-acetyl-1H-indol-1-yl)butanamido)-2-(3,5-difluorophenyl)ethyl)pyridin-3-yl)-2-fluorobenzamide (**544**):

- 5 The title compound was separated from the diastereomeric mixture of **554** by semi-preparative chiral HPLC fitted with a Chiralpak IA column running a 70:30 mixture of Hep:IPA to obtain the desired compound (RT 9.5 minutes, 12 mg): ^1H NMR (400 MHz, dmso) δ 9.24 (d, 1H), 8.69 (s, 1H), 8.26 (s, 1H), 8.09 (s, 1H), 7.64 (d, 3H), 7.56 – 7.37 (m, 4H), 7.32 (d, 1H), 7.13 (d, 2H), 6.82 (s, 1H), 6.56 (d, 2H), 5.07 (s, 2H), 2.99 (d, 2H), 2.38 (s, 3H), 2.01 (s, 2H), 0.75 (t, 3H); MS
- 10 (m/z) 599.6 $[\text{M}+\text{H}]^+$.

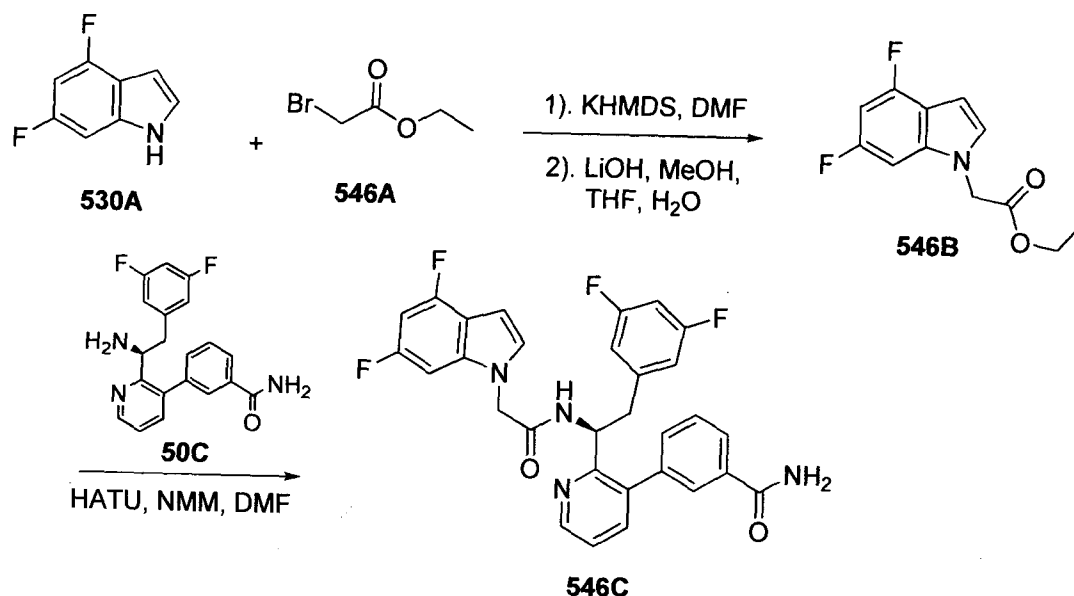
Example 545

**545**

Synthesis of (S)-5-(2-(2-(3,5-difluorophenyl)-1-(2-(6-methyl-1H-indol-1-yl)acetamido)ethyl)pyridin-3-yl)-2-fluorobenzamide (**545**):

- 15 The title compound was prepared according to the method presented in the synthesis of **56B** substituting 6-methyl-1H-indole for 1H-benzo[g]indole to provide the desired compound (7 mg, 18 %): ^1H NMR (400 MHz, dmso) δ 8.89 (d, 1H), 8.68 (d, 1H), 7.67 – 7.56 (m, 3H), 7.48 (d, 1H), 7.40 (dd, 2H), 7.34 (dd, 1H), 7.30 – 7.22 (m, 1H), 7.05 (d, 1H), 6.93 (t, 1H), 6.85 (s, 1H),
- 20 6.77 (d, 1H), 6.60 (d, 2H), 6.25 (d, 1H), 5.13 (d, 1H), 4.71 (s, 2H), 3.01 (d, 2H), 2.29 (s, 3H); MS (m/z) 543.4 $[\text{M}+\text{H}]^+$.

Example 546



Synthesis of ethyl 2-(4,6-difluoro-1H-indol-1-yl)acetate:

The title compound was prepared according to the method presented in Example 478

- 5 substituting ethyl 2-bromoacetate for **478B** and 4,6-difluoro-1H-indole for **478A** to provide the desired compound.

Synthesis of 2-(4,6-difluoro-1H-indol-1-yl)acetic acid (**546B**):

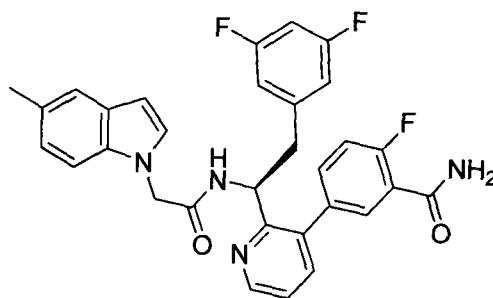
The title compound was prepared according to the method presented in Example 478

- 10 substituting ethyl 2-(4,6-difluoro-1H-indol-1-yl)acetate for **478C** to provide the desired compound: MS (m/z) 212.2 $[\text{M}+\text{H}]^+$.

Synthesis of (S)-3-(2-(1-(2-(4,6-difluoro-1H-indol-1-yl)acetamido)-2-(3,5-difluorophenyl)ethyl)pyridin-3-yl)benzamide (**546C**):

- 15 The title compound was prepared according to the method presented in the synthesis of **50C** substituting 2-(4,6-difluoro-1H-indol-1-yl)acetic acid for 2-(5-fluoro-1H-indol-3-yl)acetic acid to provide the desired compound (23 mg, 36%): ^1H NMR (400 MHz, dmsO) δ 8.96 (d, 1H), 8.72 – 8.66 (m, 1H), 7.93 (s, 1H), 7.88 (d, 1H), 7.73 (s, 1H), 7.64 (dd, 1H), 7.49 – 7.36 (m, 4H), 7.17 (d, 1H), 6.88 (t, 1H), 6.82 (d, 1H), 6.76 (t, 1H), 6.53 (d, 2H), 6.39 (d, 1H), 5.17 (dd, 1H), 4.77 (s, 2H), 2.99 (d, 2H). MS (m/z) 547.6 $[\text{M}+\text{H}]^+$.
- 20

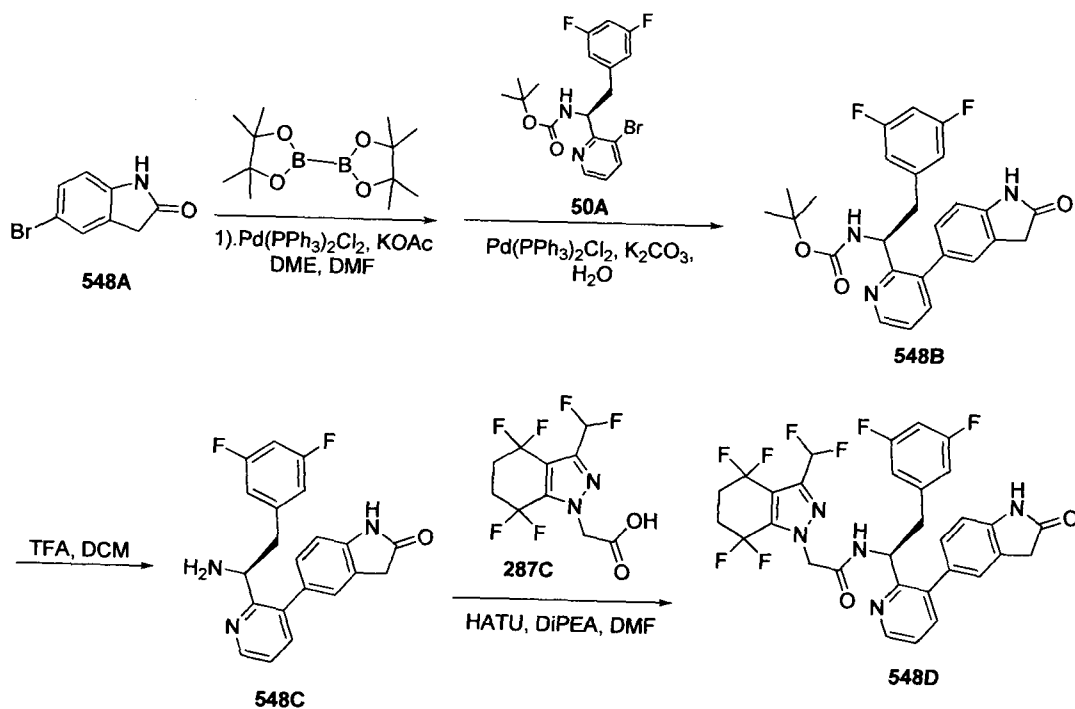
Example 547

**547**

Synthesis of (S)-5-(2-(2-(3,5-difluorophenyl)-1-(2-(5-methyl-1H-indol-1-yl)acetamido)ethyl)pyridin-3-yl)-2-fluorobenzamide (**547**):

- 5 The title compound was prepared according to the method presented in the synthesis of **56B** substituting 5-methyl-1H-indole for 1H-benzo[g]indole to provide the desired compound (7 mg, 18 %): ¹H NMR (400 MHz, dmsO) δ 8.89 (d, 1H), 8.68 (d, 1H), 7.60 (dd, 3H), 7.48 (d, 1H), 7.40 (dd, 2H), 7.26 (t, 1H), 7.23 (s, 1H), 7.07 (d, 1H), 6.95 (d, 1H), 6.90 (d, 1H), 6.79 (d, 1H), 6.61 (d, 2H), 6.21 (d, 1H), 5.12 (d, 1H), 4.70 (s, 2H), 3.01 (d, 2H), 2.30 (s, 3H); MS (*m/z*) 543.4
- 10 [M+H]⁺.

Example 548



Synthesis of (S)-tert-butyl 2-(3,5-difluorophenyl)-1-(3-(2-oxoindolin-5-yl)pyridin-2-yl)ethylcarbamate (**548B**):

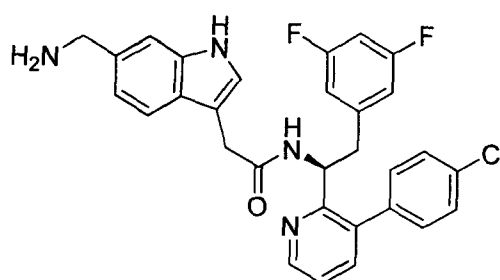
15

The title compound was prepared according to the method presented in the synthesis of **489B** substituting 5-bromoindolin-2-one for **489A** to provide the desired compound: MS (m/z) 466.3 $[M+H]^+$.

- 5 Synthesis of (S)-5-(2-(1-amino-2-(3,5-difluorophenyl)ethyl)pyridin-3-yl)indolin-2-one (**548C**):
The title compound was prepared according to the method presented in the synthesis of **50C** substituting (S)-tert-butyl 2-(3,5-difluorophenyl)-1-(3-(2-oxoindolin-5-yl)pyridin-2-yl)ethylcarbamate for **50B** to provide the desired compound: MS (m/z) 366.1 $[M+H]^+$.

- 10 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-(3-(2-oxoindolin-5-yl)pyridin-2-yl)ethyl)acetamide (**548D**):
The title compound was prepared according to the method presented in the synthesis of **61F** substituting **287C** for **61C** and **548C** for **61E** to provide the desired compound (13 mg): ^1H NMR (400 MHz, cd_3od) δ 8.64 (d, 1H), 7.63 – 7.55 (m, 1H), 7.40 (dd, 1H), 6.93 (d, 1H), 6.87 (d, 1H), 6.80 (s, 1H), 6.74 – 6.63 (m, 1H), 6.28 (d, 2H), 5.55 – 5.44 (m, 1H), 5.08 (s, 2H), 3.49 (q, 3H), 3.02 (dd, 2H), 2.64 – 2.42 (m, 4H); MS (m/z) 650.4 $[M+H]^+$.
- 15

Example 549



549

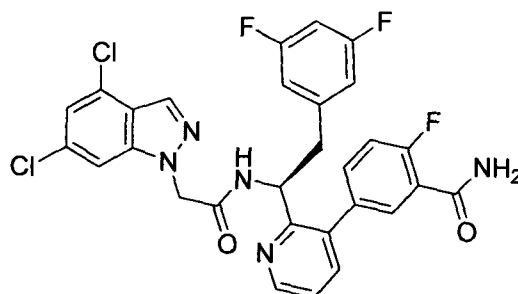
- 20 Synthesis of (S)-2-(6-(aminomethyl)-1H-indol-3-yl)-N-(1-(3-(4-chlorophenyl)pyridin-2-yl)-2-(3,5-difluorophenyl)ethyl)acetamide (**549**):

The title compound was prepared according to the method presented in the synthesis of **557** utilizing (S)-tert-butyl (3-(2-(1-(3-(4-chlorophenyl)pyridin-2-yl)-2-(3,5-

- 25 difluorophenyl)ethylamino)-2-oxoethyl)-1H-indol-6-yl)methylcarbamate to provide 18 mg of the desired compound in a 99 % yield: ^1H NMR (400 MHz, dmso) δ 10.97 (s, 1H), 8.65 (dd, 1H), 8.60 (d, 1H), 8.00 (s, 2H), 7.53 (dd, 1H), 7.46 – 7.30 (m, 5H), 7.21 (d, 2H), 7.09 (s, 1H),

6.94 (t, 2H), 6.44 (d, 2H), 5.13 (dd, 2H), 4.04 (d, 3H), 3.56 – 3.40 (m, 3H), 3.00 – 2.86 (m, 2H); MS (*m/z*) 531.4 [*M*+H]⁺.

Example 550

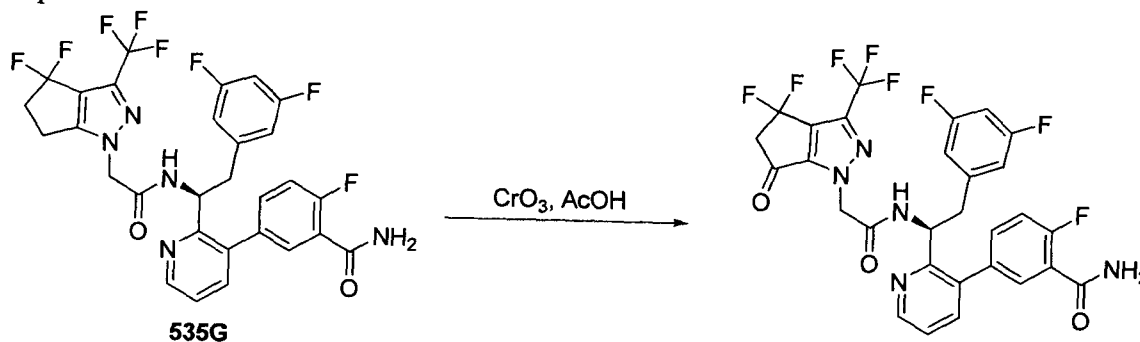


550

Synthesis of (S)-5-(2-(1-(2-(4,6-dichloro-1H-indazol-1-yl)acetamido)-2-(3,5-difluorophenyl)ethyl)pyridin-3-yl)-2-fluorobenzamide (**550**):

The title compound was prepared according to the method presented in the synthesis of **56B** substituting 4,6-dichloro-1H-indazole for 1H-benzo[*g*]indole to provide the desired compound (4 mg, 10 %): ¹H NMR (400 MHz, dmso) δ 9.11 (d, 1H), 8.69 (d, 1H), 8.40 (s, 1H), 7.67 – 7.56 (m, 4H), 7.46 – 7.37 (m, 3H), 7.34 – 7.24 (m, 1H), 7.18 (d, 1H), 6.90 (s, 1H), 6.51 (d, 2H), 5.22 – 5.05 (m, 3H), 3.00 (d, 2H); MS (*m/z*) 598.6 [*M*+H]⁺.

Example 551



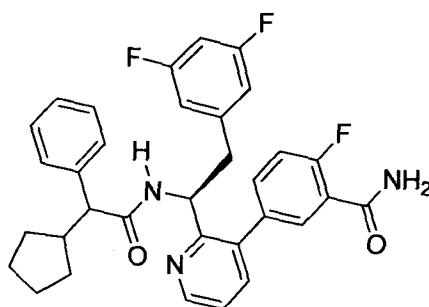
551

Synthesis of (S)-5-(2-(1-(2-(4,4-difluoro-6-oxo-3-(trifluoromethyl)-5,6-dihydrocyclopenta[*c*]pyrazol-1(4H)-yl)acetamido)-2-(3,5-difluorophenyl)ethyl)pyridin-3-yl)-2-fluorobenzamide (**551**):

A round bottom is charged with (S)-5-(2-(1-(2-(4,4-difluoro-3-(trifluoromethyl)-5,6-dihydrocyclopenta[*c*]pyrazol-1(4H)-yl)acetamido)-2-(3,5-difluorophenyl)ethyl)pyridin-3-yl)-2-fluorobenzamide (9 mg, 0.14 mmol), AcOH (2 ml), and CrO₃ (22 mg, 0.2 mmol). The mixture was stirred for 1.5 days. The reaction was concentrated then diluted with DMF, H₂O, and TFA, filtered and purified by HPLC to give the desired compound (2 mg, 24%): ¹H NMR (400 MHz,

cd_3od) δ 8.70 (s, 1H), 7.56 (d, 1H), 7.39 (dd, 2H), 7.29 (s, 1H), 7.23 – 7.15 (m, 1H), 6.64 (t, 1H), 6.29 (d, 2H), 5.38 – 5.31 (m, 1H), 5.10 (s, 2H), 3.61 (td, 1H), 3.46 (d, 1H), 3.14 – 3.03 (m, 3H); MS (m/z) 638.2 $[\text{M}+\text{H}]^+$.

5 Example 552

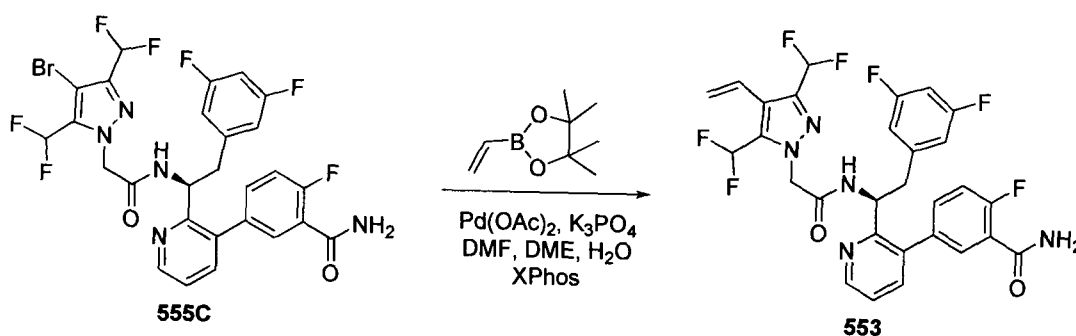


552

Synthesis of 5-(2-((1S)-1-(2-cyclopentyl-2-phenylacetamido)-2-(3,5-difluorophenyl)ethyl)pyridin-3-yl)-2-fluorobenzamide (**552**):

- 10 The title compound was prepared according to the method presented in the synthesis of **54G** substituting 2-cyclopentyl-2-phenylacetic acid for **54F** to provide the desired compound (the first peak off HPLC, 13 mg, 18 %): ^1H NMR (400 MHz, dmsO) δ 8.72 – 8.62 (m, 2H), 7.67 (d, 2H), 7.57 (dd, 1H), 7.45 (d, 2H), 7.37 (dd, 1H), 7.35 – 7.25 (m, 1H), 7.15 (ddd, 5H), 6.77 (t, 1H), 6.43 (d, 2H), 4.97 (dd, 1H), 3.28 (d, 1H), 2.89 (dd, 2H), 2.37 (s, 1H), 1.56 – 1.19 (m, 6H),
15 1.01 (s, 1H), 0.83 (d, 1H); MS (m/z) 558.6 $[\text{M}+\text{H}]^+$.

Example 553



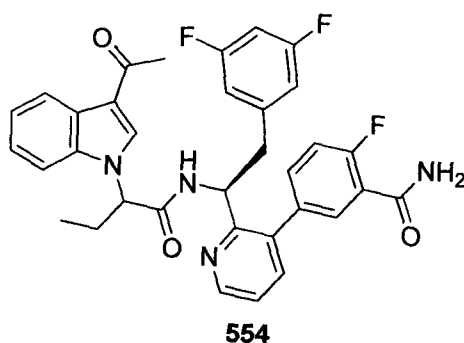
553

- 20 Synthesis of (S)-5-(2-(1-(2-(3,5-bis(difluoromethyl)-4-vinyl-1H-pyrazol-1-yl)acetamido)-2-(3,5-difluorophenyl)ethyl)pyridin-3-yl)-2-fluorobenzamide (**533**):

A 40 ml vial was charged with **555C** (100 mg, 0.15 mmol), DMF (1 ml), DME (4 ml), 4,4,5,5-tetramethyl-2-vinyl-1,3,2-dioxaborolane (0.1 ml), $\text{Pd}(\text{OAc})_2$ (10 mg, 0.01 mmol), XPhos (14mg, 0.02 mmol) and 2 N K_3PO_4 (0.3 ml). Heat the stirring mixture overnight at 86 °C. Allow the

reaction to cool then dilute with H₂O and extract 2X EtOAc. The combined organic layers were washed with brine then dried over sodium sulfate, concentrated, and purified by HPLC to give 54 mg of the desired compound. The yield was 60 %: ¹H NMR (400 MHz, cd₃od) δ 8.69 (d, 1H), 7.57 (dd, 1H), 7.42 – 7.35 (m, 2H), 7.28 (s, 1H), 7.24 – 7.17 (m, 1H), 7.08 – 6.74 (m, 3H), 6.72 (s, 1H), 6.70 – 6.59 (m, 2H), 6.30 (d, 2H), 5.49 (dd, 2H), 5.38 – 5.29 (m, 1H), 5.04 (s, 2H), 3.12 – 2.98 (m, 2H), 1.21 (t, 2H); MS (*m/z*) 605.1 [M+H]⁺.

Example 554

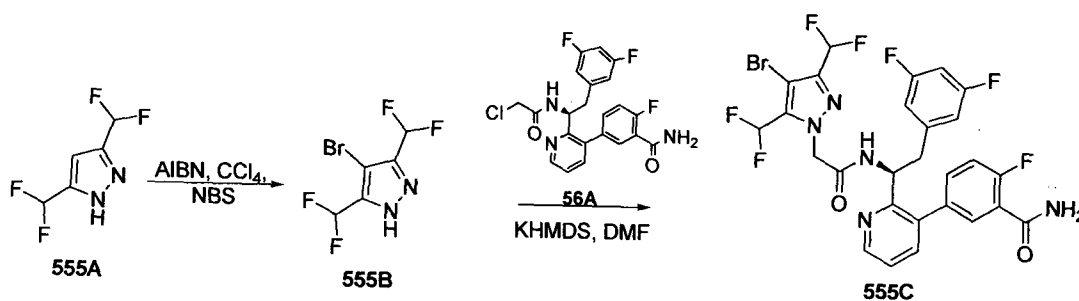


- 10 Synthesis of 5-(2-((1S)-1-(2-(3-acetyl-1H-indol-1-yl)butanamido)-2-(3,5-difluorophenyl)ethyl)pyridin-3-yl)-2-fluorobenzamide (**554**):

The title compound was prepared according to the method presented in the synthesis of **54G** substituting 2-(3-acetyl-1H-indol-1-yl)butanoic acid for **54F** to provide the desired compound (47 mg, 56%): MS (*m/z*) 599.6 [M+H]⁺.

15

Example 555



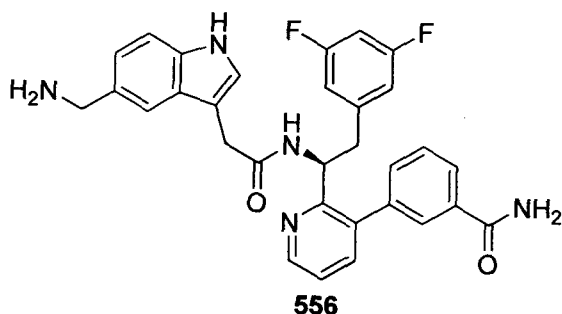
Synthesis of 4-bromo-3,5-bis(difluoromethyl)-1H-pyrazole (**555B**):

- 20 A round bottom flask was charged with 3,5-bis(difluoromethyl)-1H-pyrazole (5.3 g, 31 mmol) and CCl₄ (50 ml), NBS (8.1g, 47 mmol), and lastly AIBN (5 mg). The mixture was stirred at 90 °C over night. After cooling the mixture was filtered and concentrated and purified by flash chromatography to yield 3.3 g of the desired compound in a yield of 43 %. MS (*m/z*) 247.0 [M+H]⁺.

Synthesis of (S)-5-(2-(1-(2-(4-bromo-3,5-bis(difluoromethyl)-1H-pyrazol-1-yl)acetamido)-2-(3,5-difluorophenyl)ethyl)pyridin-3-yl)-2-fluorobenzamide (**555C**):

The title compound was prepared according to the method presented in the synthesis of **56B** substituting 4-bromo-3,5-bis(difluoromethyl)-1H-pyrazole for 1H-benzo[g]indole to provide the
 5 desired compound (780 mg, 68 %): ^1H NMR (400 MHz, dmso) δ 9.07 (d, 1H), 8.68 (d, 1H), 7.70 – 7.57 (m, 3H), 7.45 – 7.36 (m, 3H), 7.31 (d, 1H), 7.10 (s, 1H), 7.01 (d, 1H), 6.88 (d, 2H), 6.51 (d, 2H), 5.12 (s, 1H), 5.03 (s, 2H), 2.98 (d, 2H); MS (m/z) 658.4 $[\text{M}+\text{H}]^+$.

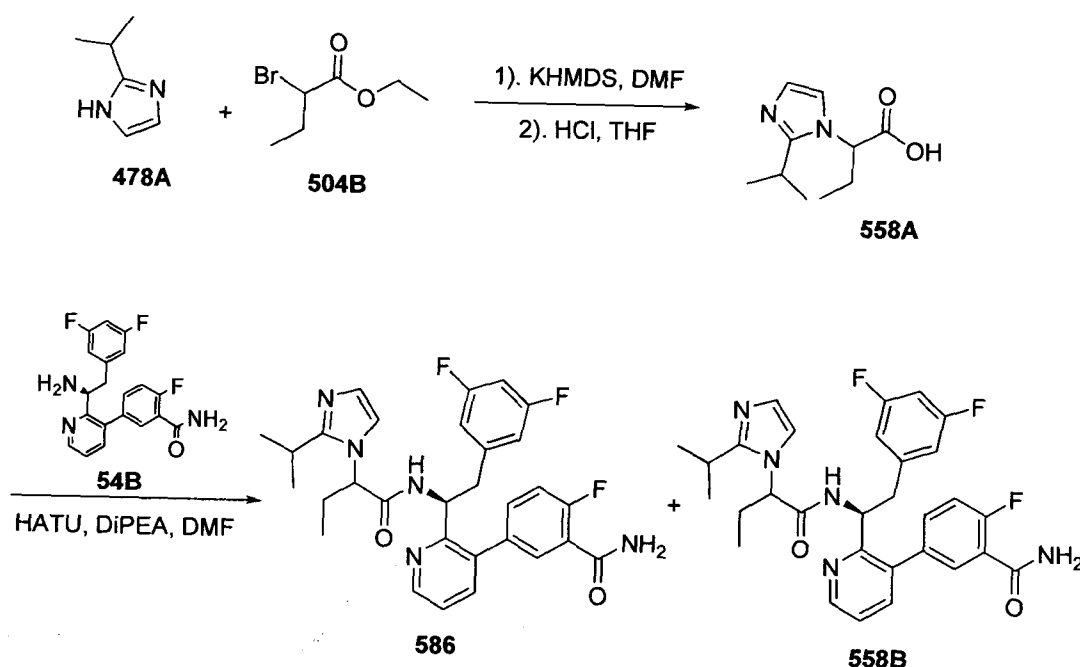
Example 556



Synthesis of (S)-3-(2-(1-(2-(5-(aminomethyl)-1H-indol-3-yl)acetamido)-2-(3,5-difluorophenyl)ethyl)pyridin-3-yl)benzamide (**556**):

The title compound was prepared according to the method presented in the synthesis of **557**
 15 utilizing **529** to provide 14 mg of the desired compound in a 99 % yield: ^1H NMR (400 MHz, dmso) δ 10.92 (s, 1H), 8.64 (dd, 1H), 8.55 (d, 1H), 7.96 (s, 3H), 7.87 (d, 1H), 7.74 (s, 1H), 7.61 (dd, 1H), 7.48 – 7.35 (m, 5H), 7.32 (d, 1H), 7.13 – 7.04 (m, 2H), 6.87 (t, 1H), 6.46 (d, 2H), 5.25 – 5.13 (m, 1H), 3.98 (d, 2H), 3.47 (d, 2H), 2.95 (d, 2H); MS (m/z) 540.1 $[\text{M}+\text{H}]^+$.

20 Examples 558 and 586



Synthesis of ethyl 2-(2-isopropyl-1H-imidazol-1-yl)butanoate:

The title compound was prepared according to the method presented in Example 478 substituting **504B** for **478B** to provide the desired compound: MS (m/z) 225.2 $[\text{M}+\text{H}]^+$.

5

Synthesis of 2-(2-isopropyl-1H-imidazol-1-yl)butanoic acid (**558A**):

A flask is charged ethyl 2-(2-isopropyl-1H-imidazol-1-yl)butanoate (1 g, 4.5 mmol), THF (5 ml) and HCl (2 ml). The reaction was stirred at reflux for 2 hours. The mixture was concentrated.

The residue was diluted with EtOAc and concentrated to give the desired compound which was used crude in the next reaction: MS (m/z) 225.2 $[\text{M}+\text{H}]^+$.

10

Synthesis of 5-(2-((1S)-2-(3,5-difluorophenyl)-1-(2-(2-isopropyl-1H-imidazol-1-yl)butanamido)ethyl)pyridin-3-yl)-2-fluorobenzamide (**586** and **558B**):

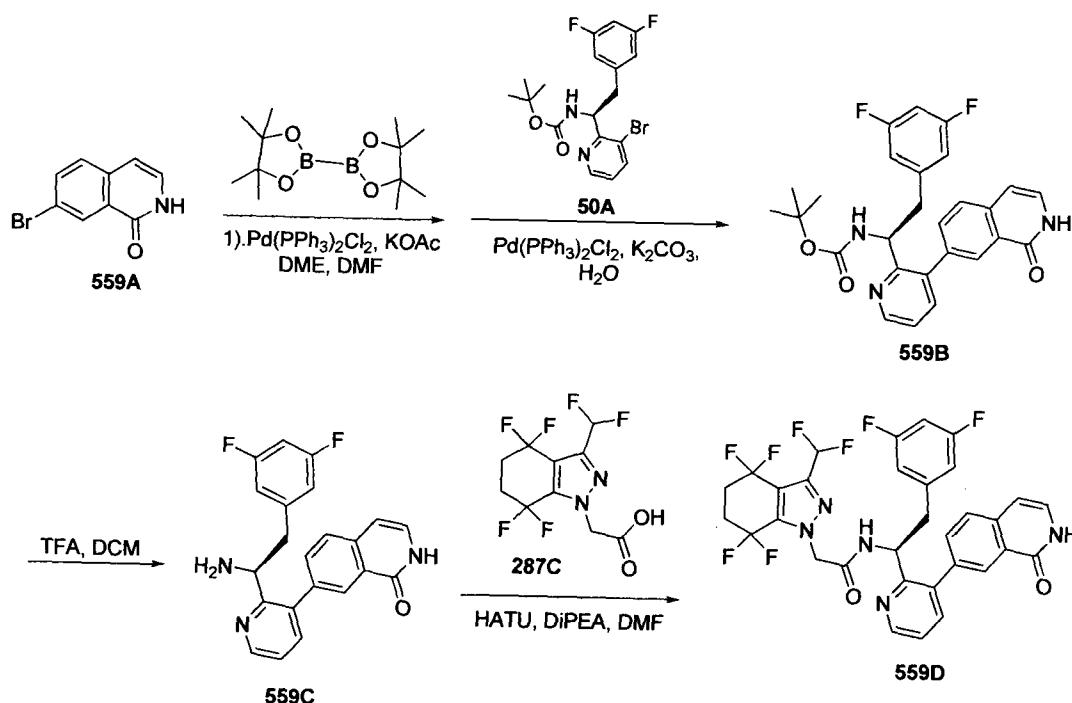
The title compounds were prepared according to the method presented in the synthesis of **54G** substituting 2-(2-isopropyl-1H-imidazol-1-yl)butanoic acid for 2-(5-(trifluoromethyl)-1H-indol-3-yl)acetic acid to provide the desired compounds (**586**, first peak off of HPLC, 4 mg, 5 %;

558B, second peak off of HPLC, 6 mg, 8 %): **586** ^1H NMR (400 MHz, dmso) δ 9.27 (d, 1H), 8.68 (d, 1H), 7.66 (dd, 3H), 7.57 – 7.53 (m, 2H), 7.42 (ddd, 4H), 6.91 (t, 1H), 6.58 (d, 2H), 5.12 (d, 1H), 4.99 (s, 1H), 3.33 – 3.19 (m, 1H), 3.10 – 2.89 (m, 2H), 1.89 (dd, 2H), 1.25 (d, 3H), 1.07 (d, 3H), 0.70 (t, 3H); MS (m/z) 550.6 $[\text{M}+\text{H}]^+$. **558C** ^1H NMR (400 MHz, dmso) δ 9.26 (d, 1H), 8.63 (d, 1H), 7.61 (ddd, 5H), 7.49 (d, 1H), 7.42 – 7.28 (m, 3H), 6.98 (t, 1H), 6.62 (d, 2H), 5.13

20

(d, 1H), 4.97 (d, 1H), 3.30 – 3.17 (m, 1H), 3.02 (d, 2H), 1.89 (dd, 2H), 1.27 (d, 3H), 0.94 (d, 3H), 0.63 (t, 3H); MS (m/z) 550.6 $[M+H]^+$.

Example 559



Synthesis of (S)-tert-butyl 2-(3,5-difluorophenyl)-1-(3-(1-oxo-1,2-dihydroisoquinolin-7-yl)pyridin-2-yl)ethylcarbamate (**559B**):

The title compound was prepared according to the method presented in the synthesis of **489B** substituting 7-bromoisoquinolin-1(2H)-one for **489A** to provide the desired compound: MS (m/z) 478.3 $[M+H]^+$.

(S)-7-(2-(1-amino-2-(3,5-difluorophenyl)ethyl)pyridin-3-yl)isoquinolin-1(2H)-one (**559C**):

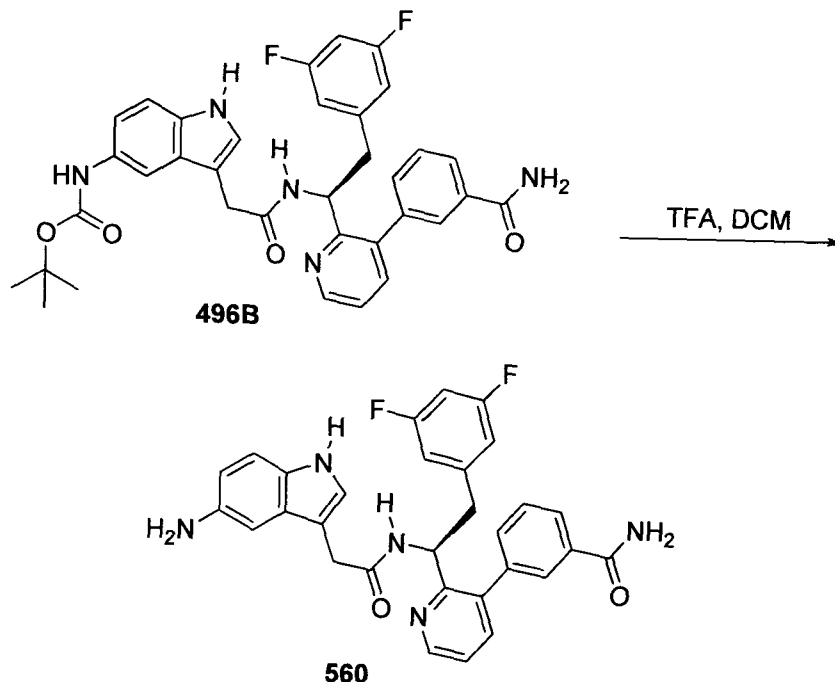
The title compound was prepared according to the method presented in the synthesis of **50C** substituting (S)-tert-butyl 2-(3,5-difluorophenyl)-1-(3-(1-oxo-1,2-dihydroisoquinolin-7-yl)pyridin-2-yl)ethylcarbamate for **50B** to provide the desired compound: MS (m/z) 378.5 $[M+H]^+$.

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-(3-(1-oxo-1,2-dihydroisoquinolin-7-yl)pyridin-2-yl)ethyl)acetamide (**559D**):

The title compound was prepared according to the method presented in the synthesis of **61F** substituting **287C** for **61C** and **559C** for **61E** to provide the desired compound (27 mg): ^1H

NMR (400 MHz, cd_3od) δ 8.72 (dd, 1H), 7.78 (s, 1H), 7.67 (ddd, 3H), 7.47 (dd, 1H), 7.20 (d, 1H), 6.86 (d, 1H), 6.73 – 6.55 (m, 2H), 6.23 (d, 2H), 5.41 (t, 1H), 5.08 (s, 2H), 3.04 (d, 2H), 2.64 – 2.36 (m, 4H); MS (m/z) 662.6 $[\text{M}+\text{H}]^+$.

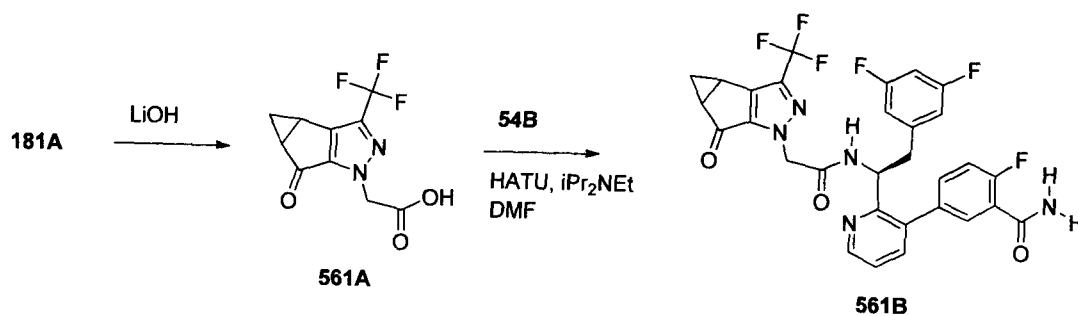
5 Example 560



Synthesis of (S)-3-(2-(1-(2-(5-amino-1H-indol-3-yl)acetamido)-2-(3,5-difluorophenyl)ethyl)pyridin-3-yl)benzamide (**560**):

The title compound was prepared according to the method presented in the synthesis of **491F** utilizing **496B** to provide 8 mg of the desired compound in a 80 % yield: ^1H NMR (400 MHz, dmso) δ 11.11 (s, 1H), 9.73 (s, 2H), 8.64 (dd, 2H), 7.99 (s, 1H), 7.86 (d, 1H), 7.72 (s, 1H), 7.60 (d, 1H), 7.40 (dt, 5H), 7.15 (s, 1H), 6.97 (d, 1H), 6.83 (t, 1H), 6.42 (d, 2H), 5.17 (d, 1H), 3.48 (dd, 3H), 2.95 (s, 2H); MS (m/z) 526.3 $[\text{M}+\text{H}]^+$.

15 Example 561



Synthesis of 2-(5-oxo-3-(trifluoromethyl)-3b,4,4a,5-tetrahydro-1H-cyclopropa[3,4]cyclopenta[1,2-c]pyrazol-1-yl)acetic acid (**561A**):

The title compound was prepared according to the method presented in the synthesis of **122F** in Example 122 utilizing **181A**.

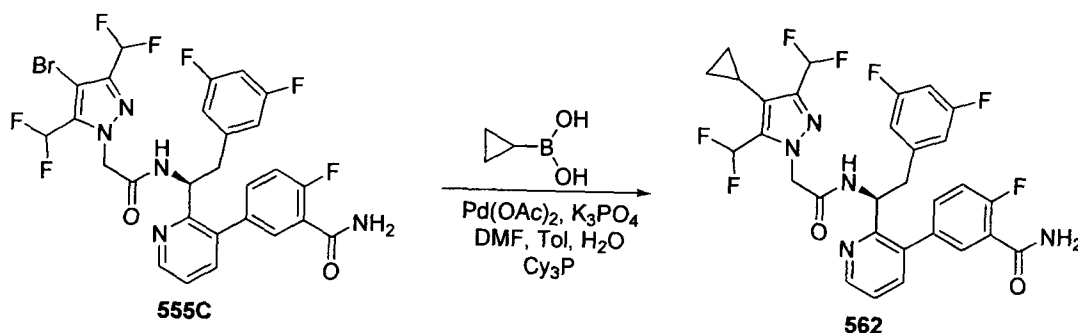
5

Synthesis of 5-(2-((1S)-2-(3,5-difluorophenyl)-1-(2-(5-oxo-3-(trifluoromethyl)-3b,4,4a,5-tetrahydro-1H-cyclopropa[3,4]cyclopenta[1,2-c]pyrazol-1-yl)acetamido)ethyl)pyridin-3-yl)-2-fluorobenzamide (**561B**):

The title compound was prepared according to the method presented in the synthesis of Example 54 utilizing **54B** and **561A**. MS (*m/z*) 559.4 [M+H]⁺. MS (*m/z*) 614.8 [M+H]⁺.

10

Example 562



Synthesis of (S)-5-(2-(1-(2-(4-cyclopropyl-3,5-bis(difluoromethyl)-1H-pyrazol-1-yl)acetamido)-2-(3,5-difluorophenyl)ethyl)pyridin-3-yl)-2-fluorobenzamide (**562**):

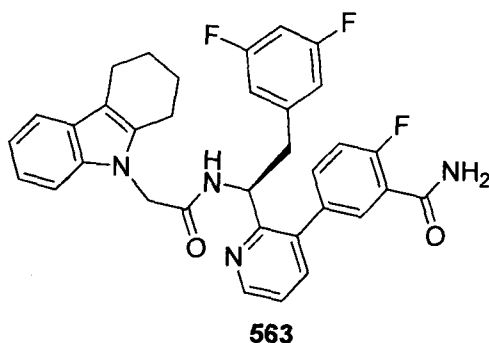
15

A 40 ml vial was charged with **555C** (100 mg, 0.15 mmol), DMF (0.5 ml), To (4 ml), cyclopropylboronic acid (60 mg, 0.7 mmol), Pd(OAc)₂ (10 mg, 0.01 mmol), Cy₃P (8 mg, 0.02 mmol), and K₃PO₄ (50 mg, 0.3 mmol) dissolved in water (0.2 ml). Heat the stirring mixture overnight at 110 °C. Allow the reaction to cool then dilute with H₂O and extract 2X EtOAc. The combined organic layers were washed with brine then dried over sodium sulfate, concentrated, and purified by HPLC to give 7 mg of the desired compound. The yield was 8 %: ¹H NMR (400 MHz, cd₃od) δ 8.68 (d, 1H), 7.57 (d, 1H), 7.39 (dd, 2H), 7.29 (s, 1H), 7.25 – 7.15 (m, 1H), 7.04 (s, 1H), 6.90 (d, 1H), 6.75 (s, 1H), 6.63 (d, 2H), 6.29 (d, 2H), 5.39 – 5.27 (m, 1H), 4.98 (s, 2H), 3.05 (dd, 3H), 1.69 (s, 1H), 0.92 (d, 2H), 0.63 (d, 2H); MS (*m/z*) 620.2 [M+H]⁺.

20

25

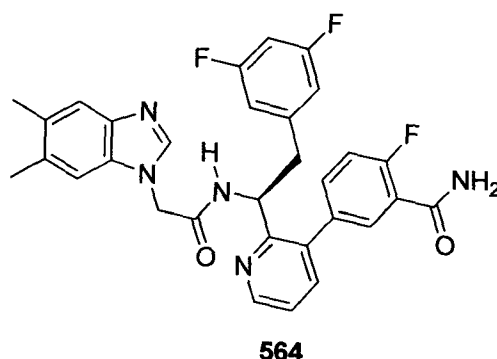
Example 563



Synthesis of (S)-5-(2-(2-(3,5-difluorophenyl)-1-(2-(3,4-dihydro-1H-carbazol-9(2H)-yl)acetamido)ethyl)pyridin-3-yl)-2-fluorobenzamide (**563**):

The title compound was prepared according to the method presented in the synthesis of **54G** substituting 2-(3,4-dihydro-1H-carbazol-9(2H)-yl)acetic acid for **54F** to provide the desired compound (36 mg, 44%): ^1H NMR (400 MHz, dmso) δ 10.86 (s, 1H), 8.69 (d, 2H), 7.65 – 7.51 (m, 5H), 7.39 (t, 2H), 7.24 (dd, 1H), 7.15 – 7.07 (m, 2H), 6.93 – 6.75 (m, 2H), 6.48 (d, 2H), 5.10 (d, 1H), 3.80 – 3.50 (m, 6H), 3.43 (s, 2H), 2.96 (t, 3H); MS (m/z) 583.7 $[\text{M}+\text{H}]^+$.

10 Example 564

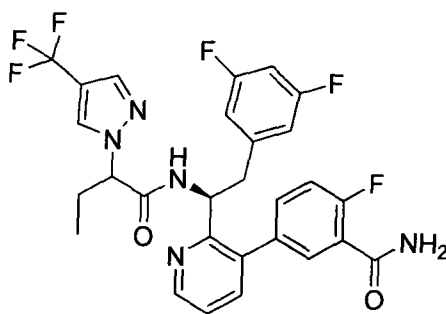


Synthesis of (S)-5-(2-(2-(3,5-difluorophenyl)-1-(2-(5,6-dimethyl-1H-benzo[d]imidazol-1-yl)acetamido)ethyl)pyridin-3-yl)-2-fluorobenzamide (**564**):

The title compound was prepared according to the method presented in the synthesis of **54G** substituting 2-(5,6-dimethyl-1H-benzo[d]imidazol-1-yl)acetic acid for **54F** to provide the desired compound (15 mg, 25 %): ^1H NMR (400 MHz, dmso) δ 9.28 (d, 1H), 9.17 (s, 1H), 8.72 (d, 1H), 7.63 (d, 3H), 7.54 (s, 1H), 7.49 (d, 1H), 7.43 (dd, 1H), 7.38 (s, 1H), 7.33 – 7.24 (m, 1H), 7.18 (s, 1H), 6.92 (s, 1H), 6.59 (d, 2H), 5.16 (d, 1H), 5.10 (s, 2H), 3.04 (d, 2H), 2.33 (s, 3H), 2.29 (s, 3H); MS (m/z) 558.7 $[\text{M}+\text{H}]^+$.

20

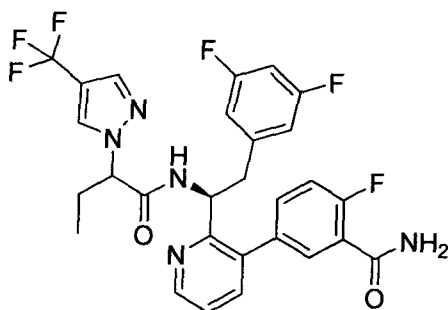
Example 565

**565**

Synthesis of 5-(2-((1S)-2-(3,5-difluorophenyl)-1-(2-(4-(trifluoromethyl)-1H-pyrazol-1-yl)butanamido)ethyl)pyridin-3-yl)-2-fluorobenzamide (**565**):

- 5 The title compound was prepared according to the method presented in the synthesis of **483D** utilizing **483C** and 4-(trifluoromethyl)-1H-pyrazole to provide 16 mg (the first peak off HPLC) of the desired compound in a 29% yield: ^1H NMR (400 MHz, dmsO) δ 9.03 (d, 1H), 8.63 (d, 1H), 8.27 (s, 1H), 7.78 (s, 1H), 7.68 (d, 2H), 7.61 (dd, 1H), 7.53 (d, 1H), 7.43 (s, 1H), 7.41 – 7.37 (m, 1H), 7.34 – 7.27 (m, 1H), 6.95 (t, 1H), 6.62 (d, 2H), 5.13 (d, 1H), 4.92 (t, 1H), 2.98 (d, 10 2H), 1.86 – 1.74 (m, 2H), 0.57 (t, 3H); MS (m/z) 576.6 $[\text{M}+\text{H}]^+$.

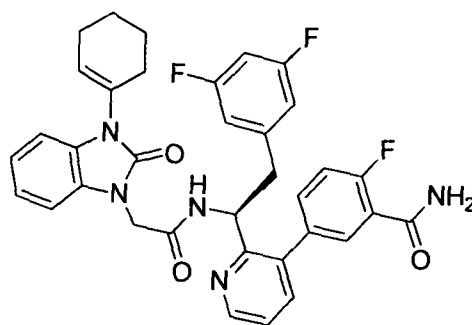
Example 566

**566**

Synthesis of 5-(2-((1S)-2-(3,5-difluorophenyl)-1-(2-(4-(trifluoromethyl)-1H-pyrazol-1-yl)butanamido)ethyl)pyridin-3-yl)-2-fluorobenzamide (**566**):

- 15 The title compound was prepared according to the method presented in the synthesis of **483D** utilizing **483C** and 4-(trifluoromethyl)-1H-pyrazole to provide 22 mg (the second peak off HPLC) of the desired compound in a 40% yield: ^1H NMR (400 MHz, dmsO) δ 8.99 (d, 1H), 8.66 (d, 1H), 8.26 (s, 1H), 7.78 (s, 1H), 7.65 (s, 2H), 7.61 – 7.57 (m, 1H), 7.47 – 7.37 (m, 3H), 7.36 – 7.27 (m, 1H), 6.84 (t, 1H), 6.46 (d, 2H), 5.10 (d, 1H), 4.93 (t, 1H), 2.97 (d, 2H), 1.94 – 1.82 (m, 20 2H), 0.67 (t, 3H); MS (m/z) 576.6 $[\text{M}+\text{H}]^+$.

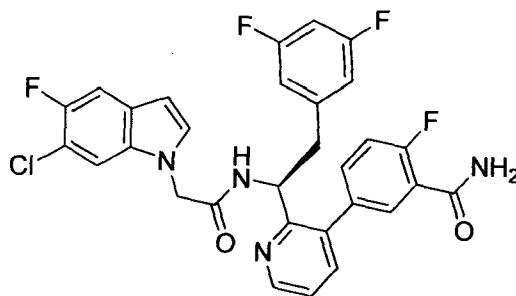
Example 567

**567**

Synthesis of (S)-5-(2-(1-(2-(3-cyclohexenyl-2-oxo-2,3-dihydro-1H-benzo[d]imidazol-1-yl)acetamido)-2-(3,5-difluorophenyl)ethyl)pyridin-3-yl)-2-fluorobenzamide (**567**):

- 5 The title compound was prepared according to the method presented in the synthesis of **54G** substituting 2-(3-cyclohexenyl-2-oxo-2,3-dihydro-1H-benzo[d]imidazol-1-yl)acetic acid for **54F** to provide the desired compound (29 mg, 57 %): ¹H NMR (400 MHz, dmso) δ 9.01 (d, 1H), 8.70 (d, 1H), 7.69 – 7.57 (m, 3H), 7.49 (d, 1H), 7.42 (dd, 2H), 7.33 – 7.23 (m, 1H), 7.02 – 6.93 (m, 3H), 6.89 (dt, 1H), 6.60 (t, 3H), 5.80 (s, 1H), 5.16 (dd, 1H), 4.37 (dd, 2H), 3.02 (d, 2H), 2.20 (d, 4H), 1.70 (d, 2H), 1.61 (d, 2H); MS (*m/z*) 626.7 [M+H]⁺.
- 10

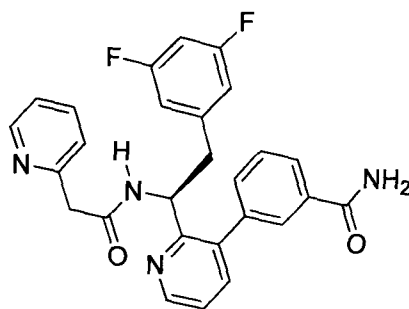
Example 568

**568**

Synthesis of (S)-5-(2-(1-(2-(6-chloro-5-fluoro-1H-indol-1-yl)acetamido)-2-(3,5-difluorophenyl)ethyl)pyridin-3-yl)-2-fluorobenzamide (**568**):

- 15 The title compound was prepared according to the method presented in the synthesis of **56B** substituting 6-chloro-5-fluoro-1H-indole for 1H-benzo[g]indole to provide the desired compound (7 mg, 17 %): ¹H NMR (400 MHz, dmso) δ 8.97 (d, 1H), 8.70 (d, 1H), 7.70 – 7.55 (m, 3H), 7.50 – 7.38 (m, 4H), 7.34 (d, 1H), 7.27 (dd, 2H), 6.90 (t, 1H), 6.55 (d, 2H), 6.36 (d, 1H), 5.13 (d, 1H), 4.78 (s, 2H), 3.00 (d, 2H); MS (*m/z*) 581.9 [M+H]⁺.
- 20

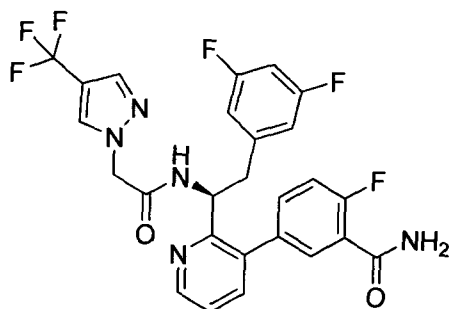
Example 569

**569**

Synthesis of (S)-3-(2-(2-(3,5-difluorophenyl)-1-(2-(pyridin-2-yl)acetamido)ethyl)pyridin-3-yl)benzamide (**569**):

The title compound was prepared according to the method presented in the synthesis of **50D** utilizing **50C** and 2-(pyridin-2-yl)acetic acid to provide 21 mg of the desired compound in a 40 % yield: ^1H NMR (400 MHz, dmso) δ 9.02 (d, 1H), 8.72 – 8.64 (m, 2H), 8.22 (t, 1H), 7.94 (s, 1H), 7.88 (d, 1H), 7.70 (dd, 2H), 7.65 (dd, 1H), 7.59 (d, 1H), 7.53 – 7.38 (m, 4H), 6.89 (t, 1H), 6.48 (d, 2H), 5.19 (dd, 1H), 3.84 (q, 2H), 3.06 – 2.91 (m, 2H); MS (m/z) 473.2 [$\text{M}+\text{H}$] $^+$.

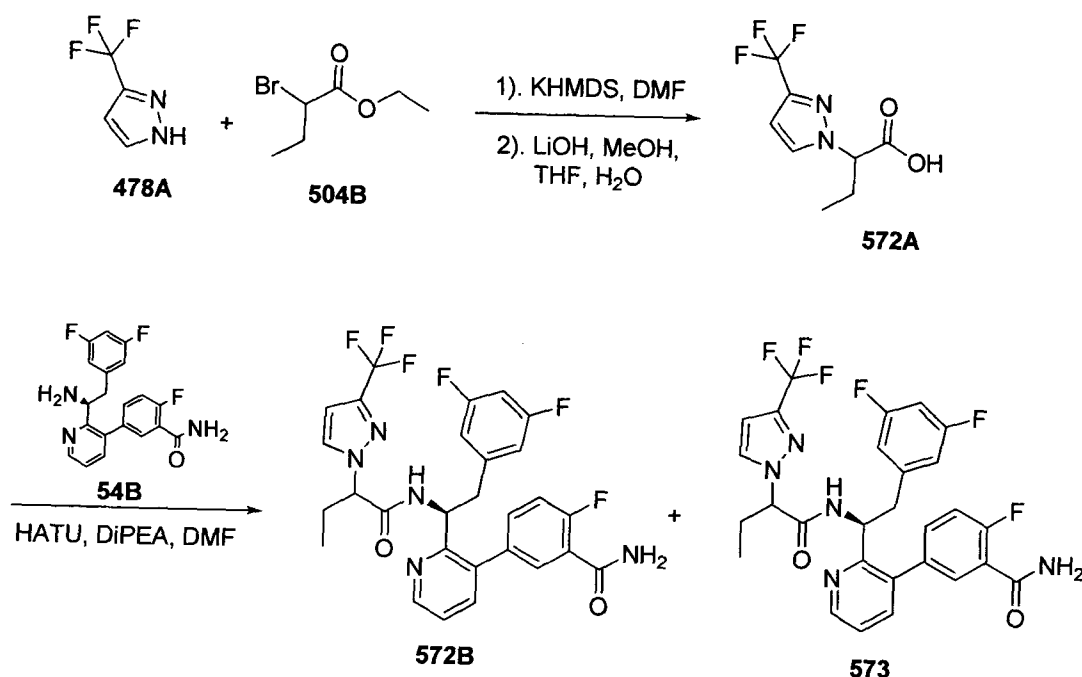
10 Example 570

**570**

Synthesis of (S)-5-(2-(2-(3,5-difluorophenyl)-1-(2-(4-(trifluoromethyl)-1H-pyrazol-1-yl)acetamido)ethyl)pyridin-3-yl)-2-fluorobenzamide (**570**):

The title compound was prepared according to the method presented in the synthesis of **56B** substituting 4-(trifluoromethyl)-1H-pyrazole for 1H-benzo[g]indole to provide the desired compound (30 mg, 78 %): ^1H NMR (400 MHz, dmso) δ 8.98 (d, 1H), 8.67 (dd, 1H), 8.17 (s, 1H), 7.78 (s, 1H), 7.65 (s, 2H), 7.60 (dd, 1H), 7.47 – 7.38 (m, 3H), 7.35 – 7.24 (m, 1H), 6.90 (t, 1H), 6.51 (d, 2H), 5.14 (dd, 1H), 4.83 (s, 2H), 2.99 (d, 2H); MS (m/z) 548.3 [$\text{M}+\text{H}$] $^+$.

20 Examples 572 and 573



Synthesis of ethyl 2-(3-(trifluoromethyl)-1H-pyrazol-1-yl)butanoate:

The title compound was prepared according to the method presented in Example 478 substituting **504B** for **478B** to provide the desired compound: MS (m/z) 251.2 $[M+H]^+$.

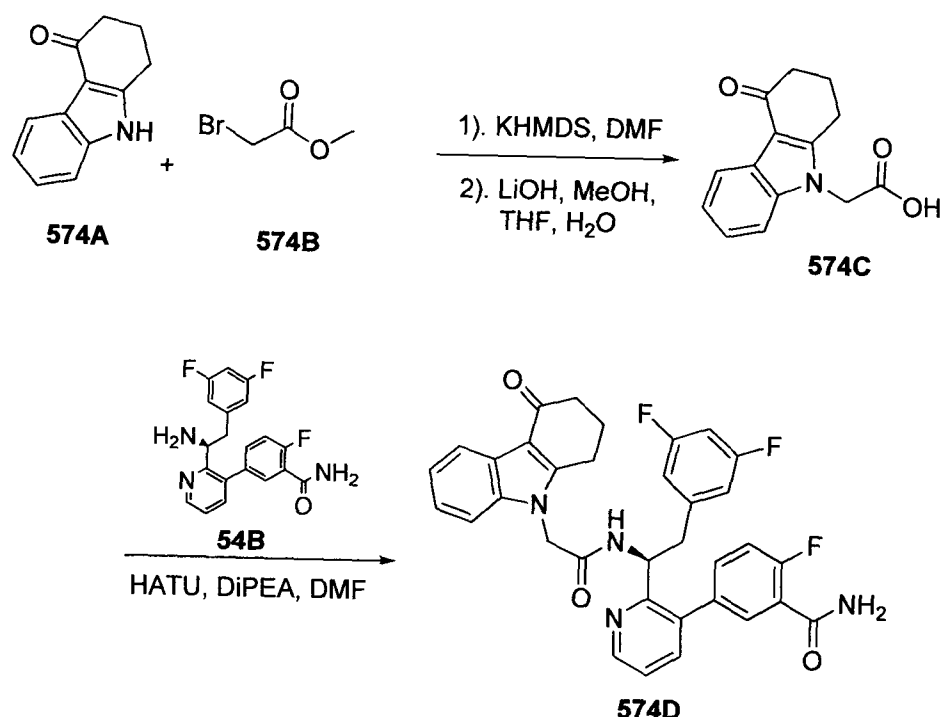
Synthesis of 2-(3-(trifluoromethyl)-1H-pyrazol-1-yl)butanoic acid (**572A**):

The title compound was prepared according to the method presented in Example 478 substituting ethyl 2-(3-(trifluoromethyl)-1H-pyrazol-1-yl)butanoate for **478C** to provide the desired compound: MS (m/z) 223.0 $[M+H]^+$.

Synthesis of 5-(2-((1S)-2-(3,5-difluorophenyl)-1-(2-(3-(trifluoromethyl)-1H-pyrazol-1-yl)butanamido)ethyl)pyridin-3-yl)-2-fluorobenzamide (**572B** and **573**):

The title compounds were prepared according to the method presented in the synthesis of **54G** substituting 2-(3-(trifluoromethyl)-1H-pyrazol-1-yl)butanoic acid for 2-(5-(trifluoromethyl)-1H-indol-3-yl)acetic acid to provide the desired compounds (**572B**, peak 1 off HPLC, 8 mg, 10 %; **573**, peak 2 off HPLC, 10.4 mg, 13 %): **572B** ^1H NMR (400 MHz, dmso) δ 9.08 (d, 1H), 8.63 (dd, 1H), 7.85 (s, 1H), 7.68 (d, 2H), 7.61 (dd, 1H), 7.52 (dd, 1H), 7.48 – 7.35 (m, 2H), 7.35 – 7.24 (m, 1H), 6.95 (t, 1H), 6.63 (d, 3H), 5.13 (dd, 1H), 4.94 (t, 1H), 2.99 (dd, 2H), 1.87 – 1.71 (m, 2H), 0.56 (t, 3H); MS (m/z) 577.1 $[M+H]^+$. **573** ^1H NMR (400 MHz, dmso) δ 9.03 (d, 1H), 8.66 (d, 1H), 7.87 (s, 1H), 7.65 (s, 2H), 7.59 (dd, 1H), 7.46 – 7.36 (m, 3H), 7.35 – 7.26 (m, 1H), 6.83 (t, 1H), 6.64 (s, 1H), 6.45 (d, 2H), 5.17 – 5.05 (m, 1H), 4.96 (t, 1H), 2.97 (d, 2H), 1.96 – 1.85 (m, 2H), 0.67 (t, 3H); MS (m/z) 577.1 $[M+H]^+$.

Example 574



Synthesis of methyl 2-(4-oxo-3,4-dihydro-1H-carbazol-9(2H)-yl)acetate:

- 5 The title compound was prepared according to the method presented in Example 478 substituting methyl 2-bromoacetate for **478B** and 2,3-dihydro-1H-carbazol-4(9H)-one for **478A** to provide the desired compound: MS (m/z) 258.4 $[\text{M}+\text{H}]^+$.

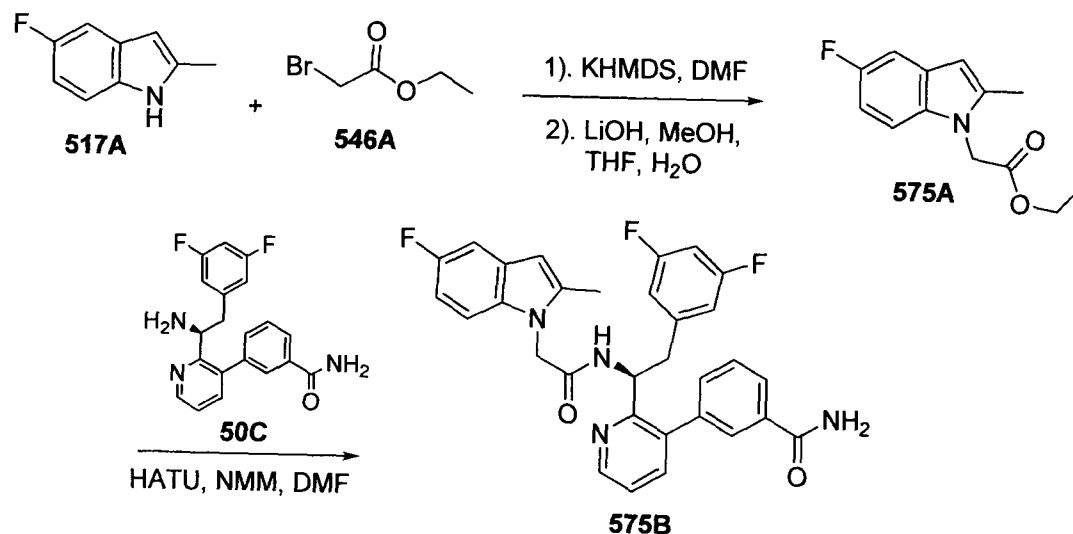
Synthesis of 2-(4-oxo-3,4-dihydro-1H-carbazol-9(2H)-yl)acetic acid (**574C**):

- 10 The title compound was prepared according to the method presented in Example 478 substituting methyl 2-(4-oxo-3,4-dihydro-1H-carbazol-9(2H)-yl)acetate for **478C** to provide the desired compound: MS (m/z) 244.3 $[\text{M}+\text{H}]^+$.

Synthesis of (S)-5-(2-(2-(3,5-difluorophenyl)-1-(2-(4-oxo-3,4-dihydro-1H-carbazol-9(2H)-yl)acetamido)ethyl)pyridin-3-yl)-2-fluorobenzamide (**574D**):

- 15 The title compound was prepared according to the method presented in the synthesis of **54G** substituting 2-(4-oxo-3,4-dihydro-1H-carbazol-9(2H)-yl)acetic acid for **54F** to provide the desired compound (18 mg, 28): ^1H NMR (400 MHz, dmso) δ 9.12 (d, 1H), 8.70 (dd, 1H), 7.93 – 7.87 (m, 1H), 7.69 – 7.58 (m, 3H), 7.53 (dd, 1H), 7.42 (dd, 2H), 7.32 – 7.24 (m, 1H), 7.21 (d, 1H), 7.16 – 7.04 (m, 2H), 6.97 (t, 1H), 6.65 (d, 2H), 5.16 (dd, , 1H), 4.81 (s, 2H), 3.03 (d, 2H), 2.74 (d, 1H), 2.68 – 2.57 (m, 1H), 2.34 (d, 2H), 2.00 (s, 2H); MS (m/z) 597.7 $[\text{M}+\text{H}]^+$.
- 20

Example 575



Synthesis of ethyl 2-(5-fluoro-2-methyl-1H-indol-1-yl)acetate:

The title compound was prepared according to the method presented in Example 478

- 5 substituting ethyl 2-bromoacetate for 478B and 5-fluoro-2-methyl-1H-indole for 478A to provide the desired compound.

Synthesis of 2-(5-fluoro-2-methyl-1H-indol-1-yl)acetic acid (575A):

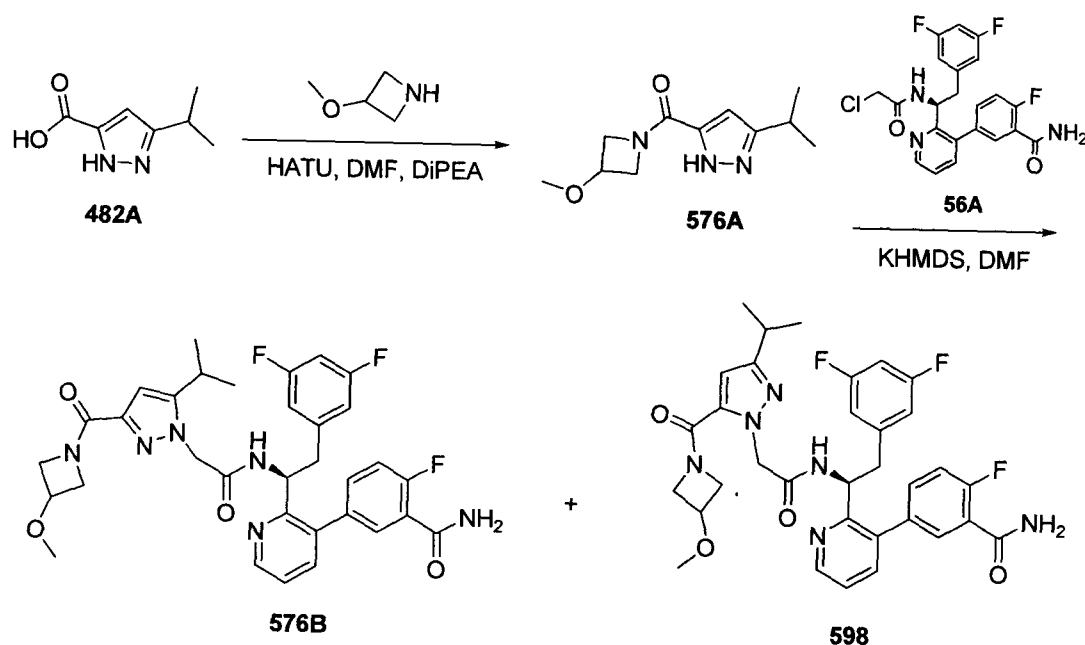
The title compound was prepared according to the method presented in Example 478

- 10 substituting ethyl 2-(5-fluoro-2-methyl-1H-indol-1-yl)acetate for 478C to provide the desired compound: MS (*m/z*) 208.3 [M+H]⁺.

Synthesis of (S)-3-(2-(2-(3,5-difluorophenyl)-1-(2-(5-fluoro-2-methyl-1H-indol-1-yl)acetamido)ethyl)pyridin-3-yl)benzamide (575B):

- 15 The title compound was prepared according to the method presented in the synthesis of 50C substituting 2-(5-fluoro-2-methyl-1H-indol-1-yl)acetic acid for 2-(5-fluoro-1H-indol-3-yl)acetic acid to provide the desired compound (8 mg, 13%): ¹H NMR (400 MHz, dmso) δ 8.91 (d, 1H), 8.68 (dd, 1H), 7.94 (s, 1H), 7.88 (d, 1H), 7.75 (s, 1H), 7.64 (dd, 1H), 7.49 – 7.36 (m, 4H), 7.11 – 7.03 (m, 2H), 6.95 (t, 1H), 6.73 (dd, 1H), 6.56 (d, 2H), 6.09 (s, 1H), 5.16 (dd, 1H), 4.70 (s, 2H), 2.98 (d, 2H), 2.13 (s, 3H); MS (*m/z*) 543.5 [M+H]⁺.
- 20

Examples 576 and 598



Synthesis of (3-isopropyl-1H-pyrazol-5-yl)(3-methoxyazetidin-1-yl)methanone (**576A**):

The title compound was prepared according to the method presented in Example **482**

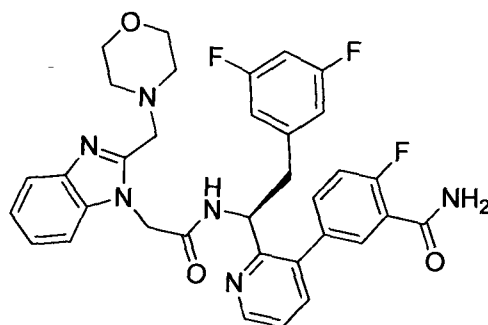
5 substituting 3-methoxyazetidine for cyclopropanamine to provide the desired compound: MS (m/z) 224.2 $[M+H]^+$.

10 (S)-5-(2-(2-(3,5-difluorophenyl)-1-(2-(5-isopropyl-3-(3-methoxyazetidine-1-carbonyl)-1H-pyrazol-1-yl)acetamido)ethyl)pyridin-3-yl)-2-fluorobenzamide (**576B**) and (S)-5-(2-(2-(3,5-difluorophenyl)-1-(2-(3-isopropyl-5-(3-methoxyazetidine-1-carbonyl)-1H-pyrazol-1-yl)acetamido)ethyl)pyridin-3-yl)-2-fluorobenzamide (**598**):

The title compound was prepared according to the method presented in the synthesis of **56B** substituting (3-isopropyl-1H-pyrazol-5-yl)(3-methoxyazetidin-1-yl)methanone for 1H-

15 benzo[g]indole to provide the desired compounds (**576B**, 7 mg, 16 %; **598**, 9 mg, 20%): **576B** ^1H NMR (400 MHz, dmso) δ 8.65 (s, 1H), 8.62 – 8.52 (m, 1H), 7.68 – 7.55 (m, 3H), 7.39 (dd, 3H), 7.28 (d, 1H), 6.88 (s, 1H), 6.43 (d, 3H), 5.12 (d, 1H), 4.98 (s, 2H), 4.44 – 4.35 (m, 1H), 4.16 (s, 4H), 3.18 (s, 3H), 2.95 (s, 2H), 2.85 – 2.74 (m, 1H), 1.13 (d, 6H); MS (m/z) 635.5 $[M+H]^+$. **598** ^1H NMR (400 MHz, dmso) δ 8.79 (s, 1H), 8.66 (d, 1H), 7.73 – 7.59 (m, 3H), 7.50 (s, 1H), 7.44 – 7.36 (m, 2H), 7.36 – 7.27 (m, 1H), 6.93 (s, 1H), 6.58 (d, 2H), 6.33 (s, 1H), 5.18 (s, 1H), 4.73 (s, 2H), 4.42 (s, 1H), 4.12 (d, 4H), 3.18 (s, 3H), 2.99 (d, 2H), 2.70 – 2.56 (m, 1H), 20 1.00 (t, 6H); MS (m/z) 635.5 $[M+H]^+$.

Example 577

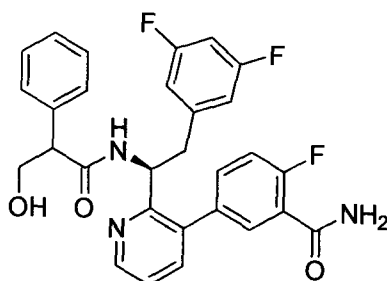
**577**

Synthesis of (S)-5-(2-(2-(3,5-difluorophenyl)-1-(2-(2-(morpholinomethyl)-1H-benzo[d]imidazol-1-yl)acetamido)ethyl)pyridin-3-yl)-2-fluorobenzamide (**577**):

- 5 The title compound was prepared according to the method presented in the synthesis of **54G** substituting 2-(2-(morpholinomethyl)-1H-benzo[d]imidazol-1-yl)acetic acid for **54F** to provide the desired compound (29 mg, 43 %): ^1H NMR (400 MHz, dmso) δ 9.34 (d, 1H), 8.72 (d, 1H), 7.64 (d, 4H), 7.55 (d, 1H), 7.52 – 7.36 (m, 3H), 7.31 – 7.21 (m, 3H), 6.94 (t, 1H), 6.64 (d, 2H), 5.15 (d, 1H), 5.02 (s, 2H), 4.45 (s, 2H), 3.69 (s, 4H), 3.05 (d, 6H); MS (m/z) 629.4 [$\text{M}+\text{H}$] $^+$.

10

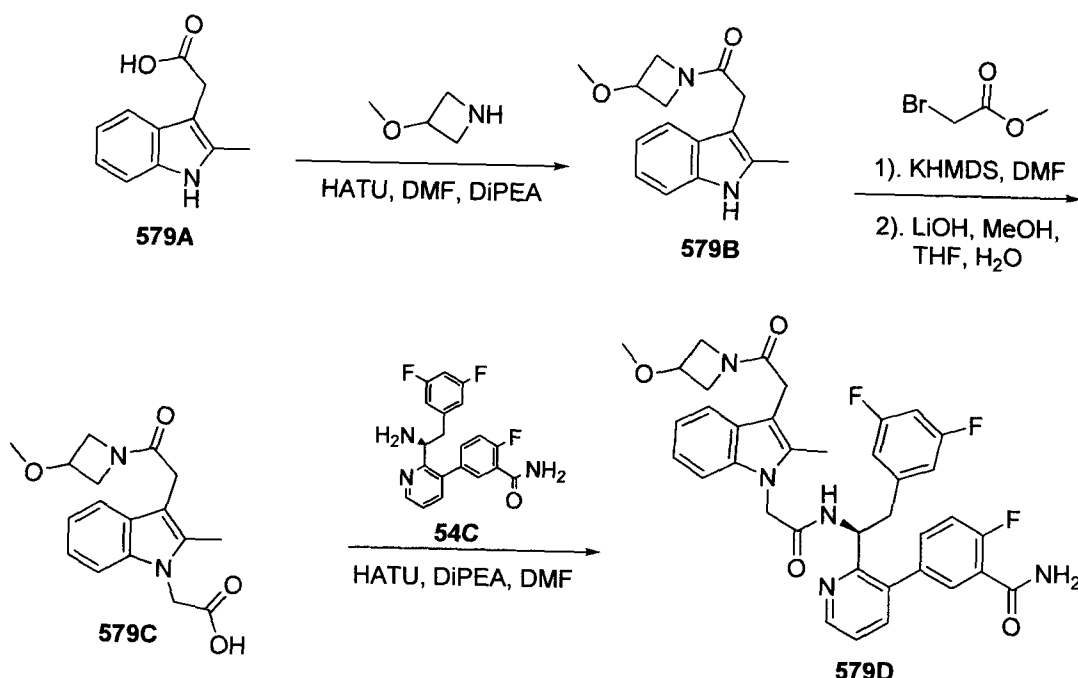
Example 578

**578**

Synthesis of 5-(2-((1S)-2-(3,5-difluorophenyl)-1-(3-hydroxy-2-phenylpropanamido)ethyl)pyridin-3-yl)-2-fluorobenzamide (**578**):

- 15 The title compound was prepared according to the method presented in the synthesis of **54G** substituting 43-hydroxy-2-phenylpropanoic acid for 2-(5-(trifluoromethyl)-1H-indol-3-yl)acetic acid to provide the desired compound (12 mg, 17 %): MS (m/z) 520.4 [$\text{M}+\text{H}$] $^+$.

Example 579



Synthesis of 1-(3-methoxyazetidin-1-yl)-2-(2-methyl-1H-indol-3-yl)ethanone (**579B**):

The title compound was prepared according to the method presented in Example **482** substituting 2-(2-methyl-1H-indol-3-yl)acetic acid for **482A** and 3-methoxyazetidine for cyclopropanamine to provide the desired compound: MS (m/z) 259.4 $[M+H]^+$.

Synthesis methyl 2-(3-(2-(3-methoxyazetidin-1-yl)-2-oxoethyl)-2-methyl-1H-indol-1-yl)acetate:

The title compound was prepared according to the method presented in Example **478** substituting methyl 2-bromoacetate for **478B** and 1-(3-methoxyazetidin-1-yl)-2-(2-methyl-1H-indol-3-yl)ethanone for **478A** to provide the desired compound: MS (m/z) 330.3 $[M+H]^+$.

Synthesis of 2-(3-(2-(3-methoxyazetidin-1-yl)-2-oxoethyl)-2-methyl-1H-indol-1-yl)acetic acid (**579C**):

The title compound was prepared according to the method presented in Example **478** substituting methyl 2-(3-(2-(3-methoxyazetidin-1-yl)-2-oxoethyl)-2-methyl-1H-indol-1-yl)acetate for **478C** to provide the desired compound: MS (m/z) 317.9 $[M+H]^+$.

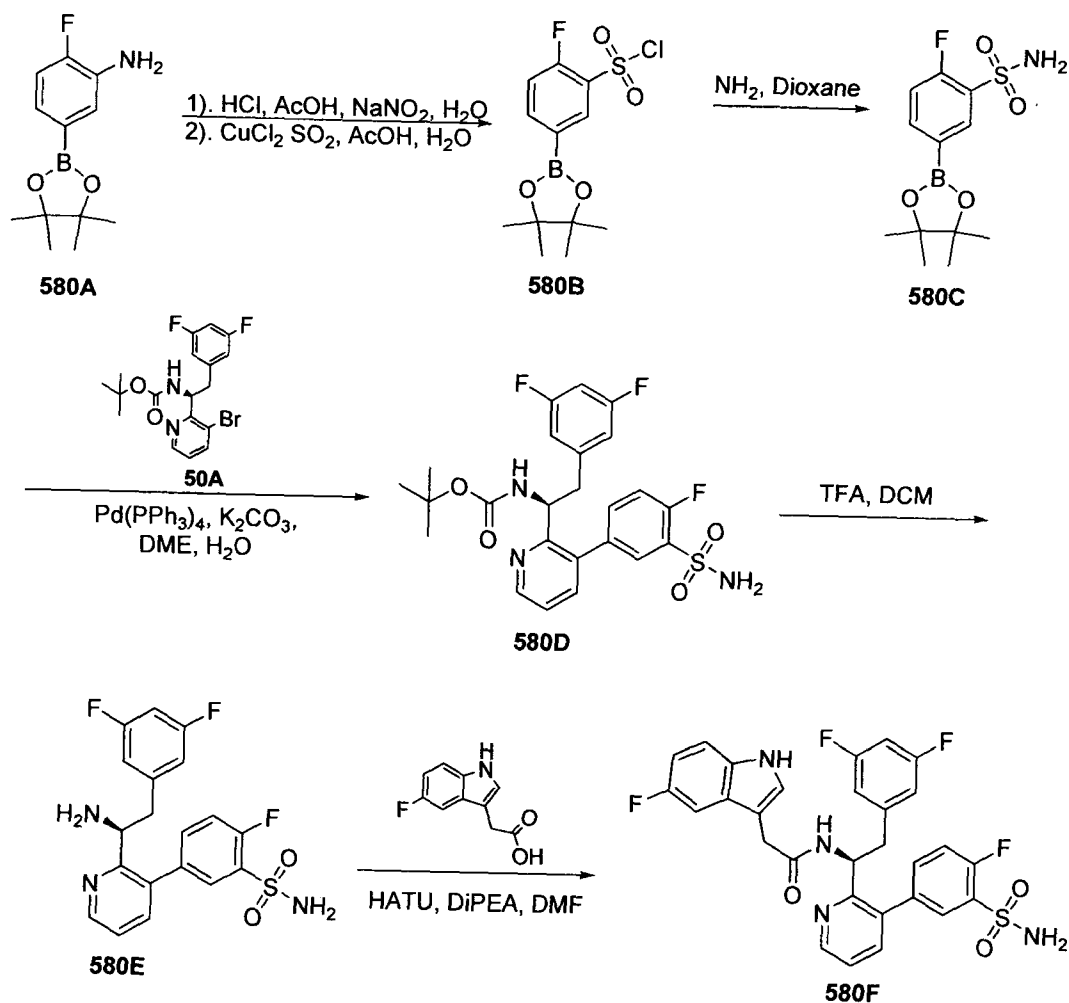
Synthesis of (S)-5-(2-(2-(3,5-difluorophenyl)-1-(2-(3-(2-(3-methoxyazetidin-1-yl)-2-oxoethyl)-2-methyl-1H-indol-1-yl)acetamido)ethyl)pyridin-3-yl)-2-fluorobenzamide(**579D**):

The title compound was prepared according to the method presented in the synthesis of **54G** substituting 2-(3-(2-(3-methoxyazetidin-1-yl)-2-oxoethyl)-2-methyl-1H-indol-1-yl)acetic acid for **54F** to provide the desired compound (3 mg, 4 %): ^1H NMR (400 MHz, dms) δ 8.92 (d,

1H), 8.68 (d, 1H), 7.60 (s, 3H), 7.47 (s, 1H), 7.45 – 7.36 (m, 2H), 7.35 (d, 1H), 7.30 – 7.24 (m, 1H), 7.06 (d, 1H), 7.00 – 6.84 (m, 3H), 6.60 (s, 2H), 5.14 (s, 1H), 4.69 (s, 2H), 4.16 (s, 1H), 4.07 (s, 1H), 3.92 (d, 2H), 3.87 – 3.79 (m, 1H), 3.40 (s, 2H), 3.11 (s, 3H), 3.00 (d, 2H), 2.10 (d, 3H); MS (*m/z*) 670.5 [*M*+H]⁺.

5

Example 580



Synthesis of 2-fluoro-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzene-1-sulfonyl chloride (**580B**):

- 10 A round bottom was charged with 2-fluoro-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)aniline (1 g, 4.2 mmol), HCl (1.5 ml), AcOH (4.4 ml), and cool the reaction to 0 °C. To the cooled stirring reaction slowly add sodium nitrate (318 mg, 4.6 mmol) dissolved in H₂O (0.7 ml). Remove the ice bath and stir at RT for 15 minutes and cool to 0 °C. Make a mixture of CuCl₂ (373 mg, 2.2 mmol) and H₂O (0.44 ml) and add it to a cooled (0 °C) mixture of SO₂
- 15 saturated in AcOH (3.7 ml). Then add the Cu mixture into the aniline mixture and allow to warm

to RT over 1 hour. Ice/water was added and the solution was filtered. The cake was dried under vacuum to give the desired compound (1 g, 74%).

Synthesis of 2-fluoro-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzenesulfonamide
5 (580C):

A round bottom was charged with 2-fluoro-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzene-1-sulfonyl chloride (1 g, 3 mmol) and 4 N ammonia in dioxane (5 ml). The mixture was stirred at RT for 2 hours. The reaction was concentrated and used crude the next reaction.

10 Synthesis of (S)-tert-butyl 2-(3,5-difluorophenyl)-1-(3-(4-fluoro-3-sulfamoylphenyl)pyridin-2-yl)ethylcarbamate (580D):

The title compound was prepared according to the method presented in Example 50 substituting 2-fluoro-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)benzenesulfonamide for 3-carbamoylphenylboronic acid to provide the desired compound: MS (*m/z*) 508.1 [M+H]⁺.

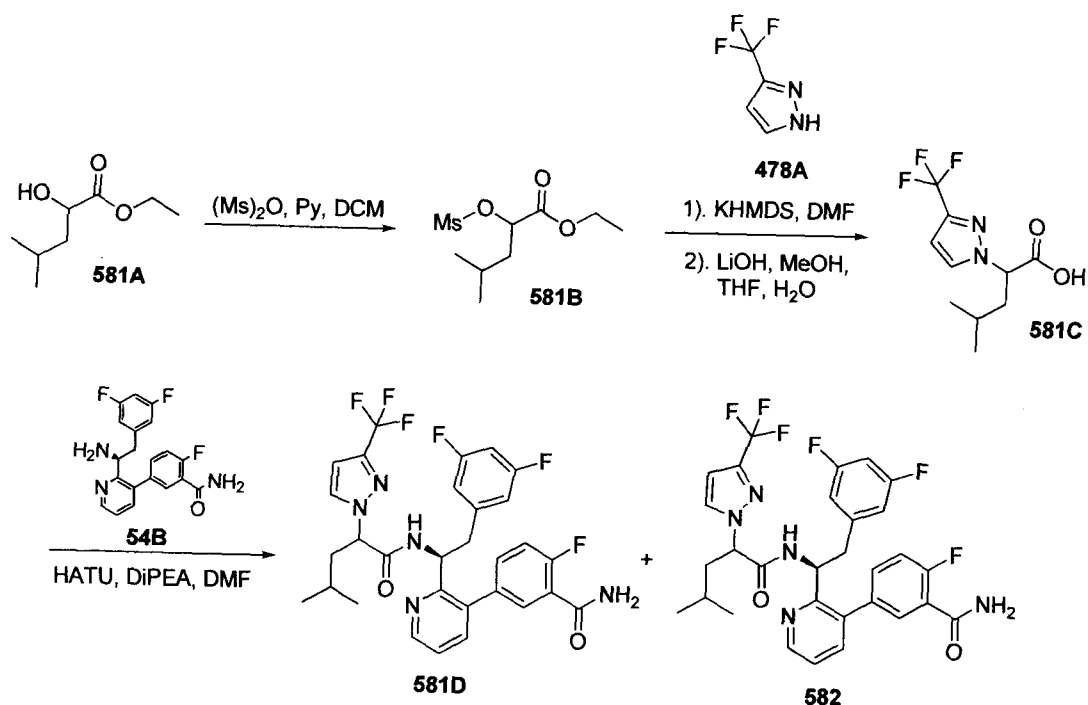
15 Synthesis of (S)-5-(2-(1-amino-2-(3,5-difluorophenyl)ethyl)pyridin-3-yl)-2-fluorobenzenesulfonamide (580E):

The title compound was prepared according to the method presented in Example 50 substituting (S)-tert-butyl 2-(3,5-difluorophenyl)-1-(3-(4-fluoro-3-sulfamoylphenyl)pyridin-2-yl)ethylcarbamate for 50B to provide the desired compound: MS (*m/z*) 408.2 [M+H]⁺.

Synthesis of (S)-N-(2-(3,5-difluorophenyl)-1-(3-(4-fluoro-3-sulfamoylphenyl)pyridin-2-yl)ethyl)-2-(5-fluoro-1H-indol-3-yl)acetamide (580F):

25 The title compound was prepared according to the method presented in the synthesis of 50D substituting (S)-5-(2-(1-amino-2-(3,5-difluorophenyl)ethyl)pyridin-3-yl)-2-fluorobenzenesulfonamide for 50C to provide the desired compound (14 mg): ¹H NMR (400 MHz, dmso) δ 8.83 (d, 1H), 8.67 (d, 1H), 7.70 – 7.58 (m, 3H), 7.53 (d, 1H), 7.45 (s, 1H), 7.41 (dd, 1H), 7.28 (dd, 2H), 7.07 (d, 1H), 6.95 (t, 1H), 6.88 (dd, 2H), 6.63 (d, 2H), 5.15 (dd, 1H), 4.60 (s, 2H), 2.99 (d, 2H); MS (*m/z*) 583.6 [M+H]⁺.

30 Examples 581 and 582



Synthesis of ethyl 4-methyl-2-(methanesulfonyloxy)pentanoate (**581B**):

A flask is charged ethyl 2-hydroxy-4-methylpentanoate (5 g, 31 mmol), DCM (100 ml), pyridine (3 ml, 37 mmol), and methanesulfonyl anhydride (6.5g, 37 mmol). The reaction was stirred until
 5 done by TLC. The mixture was filtered to remove solids. The mother liquor was diluted with H_2O and extract 2X with DCM. The organic layer was dried over sodium sulfate, concentrated, and purified by flash chromatography to give the desired compound (5 g, 67%): MS (m/z) 238.9 $[\text{M}+\text{H}]^+$.

10 Synthesis of ethyl 4-methyl-2-(3-(trifluoromethyl)-1H-pyrazol-1-yl)pentanoate:

The title compound was prepared according to the method presented in Example 478 substituting ethyl 4-methyl-2-(methanesulfonyloxy)pentanoate for **478B** to provide the desired compound: MS (m/z) 279.2 $[\text{M}+\text{H}]^+$.

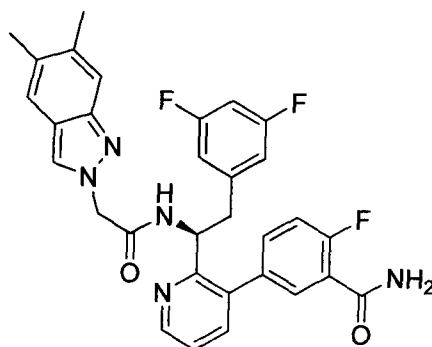
15 Synthesis of 4-methyl-2-(3-(trifluoromethyl)-1H-pyrazol-1-yl)pentanoic acid (**581C**):

The title compound was prepared according to the method presented in Example 478 substituting ethyl 4-methyl-2-(3-(trifluoromethyl)-1H-pyrazol-1-yl)pentanoate for **478C** to provide the desired compound: MS (m/z) 251.0 $[\text{M}+\text{H}]^+$.

20 Synthesis of 5-(2-((1S)-2-(3,5-difluorophenyl)-1-(4-methyl-2-(3-(trifluoromethyl)-1H-pyrazol-1-yl)pentanamido)ethyl)pyridin-3-yl)-2-fluorobenzamide (**581D** and **582**):

The title compounds were prepared according to the method presented in the synthesis of **54G** substituting 4-methyl-2-(3-(trifluoromethyl)-1H-pyrazol-1-yl)pentanoic acid for 2-(5-(trifluoromethyl)-1H-indol-3-yl)acetic acid to provide the desired compounds (**581D**, peak 1 off HPLC, 8 mg, 10 %; **582**, peak 2 off HPLC, 12 mg, 15 %): **581D** ^1H NMR (400 MHz, dmso) δ 9.19 (d, 1H), 8.63 (d, 1H), 7.84 (s, 1H), 7.70 (d, 2H), 7.60 (dd, 2H), 7.45 (s, 1H), 7.39 (dd, 1H), 7.37 – 7.28 (m, 1H), 6.99 (s, 1H), 6.69 (d, 2H), 6.62 (s, 1H), 5.19 – 5.02 (m, 2H), 3.00 (d, 2H), 1.62 (s, 1H), 1.55 – 1.42 (m, 1H), 0.92 (s, 1H), 0.73 (dd, 6H); MS (m/z) 605.0 $[\text{M}+\text{H}]^+$. **582** ^1H NMR (400 MHz, dmso) δ 9.03 (d, 1H), 8.65 (d, 1H), 7.88 (s, 1H), 7.65 (s, 2H), 7.58 (d, 1H), 7.46 – 7.38 (m, 3H), 7.38 – 7.26 (m, 1H), 6.83 (d, 1H), 6.63 (s, 1H), 6.44 (d, 2H), 5.12 (dd, 2H), 2.97 (d, 2H), 1.82 (s, 1H), 1.65 (d, 1H), 1.11 (s, 1H), 0.77 (d, 6H); MS (m/z) 605.3 $[\text{M}+\text{H}]^+$.

Example 583

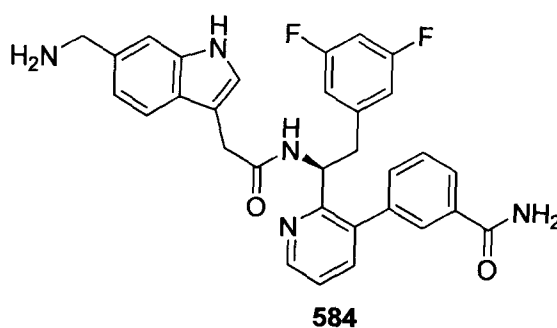


583

15 Synthesis of (S)-5-(2-(2-(3,5-difluorophenyl)-1-(2-(5,6-dimethyl-2H-indazol-2-yl)acetamido)ethyl)pyridin-3-yl)-2-fluorobenzamide (**583**):

The title compound was prepared according to the method presented in the synthesis of **56B** substituting 5,6-dimethyl-1H-indazole for 1H-benzo[g]indole to provide the desired compound (5.4 mg, 15%): ^1H NMR (400 MHz, dmso) δ 8.96 (d, 1H), 8.68 (d, 1H), 7.98 (s, 1H), 7.66 – 7.54 (m, 3H), 7.39 (dd, 4H), 7.25 (t, 2H), 6.90 (s, 1H), 6.49 (d, 2H), 5.14 (d, 1H), 5.00 (s, 2H), 2.99 (d, 2H), 2.24 (d, 6H); MS (m/z) 558.4 $[\text{M}+\text{H}]^+$.

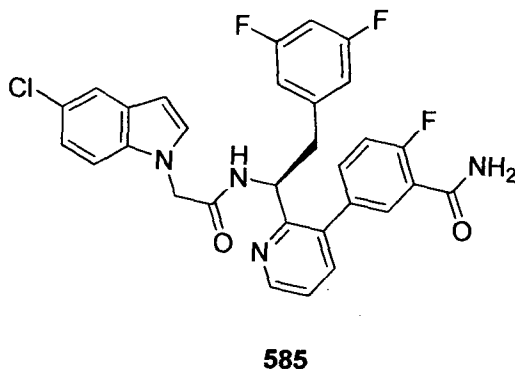
Example 584



Synthesis of (S)-3-(2-(1-(2-(6-(aminomethyl)-1H-indol-3-yl)acetamido)-2-(3,5-difluorophenyl)ethyl)pyridin-3-yl)benzamide (**584**):

The title compound was prepared according to the method presented in the synthesis of **557** utilizing (S)-tert-butyl (3-(2-(1-(3-(3-carbamoylphenyl)pyridin-2-yl)-2-(3,5-difluorophenyl)ethylamino)-2-oxoethyl)-1H-indol-6-yl)methylcarbamate to provide 22 mg of the desired compound in a 99 % yield ¹H NMR (400 MHz, dmso) δ 10.96 (s, 1H), 8.70 – 8.65 (m, 1H), 8.62 (d, 1H), 8.00 (s, 2H), 7.95 (s, 1H), 7.86 (d, 1H), 7.75 (s, 1H), 7.61 (dd, 1H), 7.41 (ddd, 4H), 7.30 (d, 1H), 7.06 (s, 1H), 6.91 (d, 2H), 6.50 (d, 2H), 5.18 (dd, , 2H), 4.03 (d, 2H), 3.47 (d, 2H), 2.95 (d, 2H); MS (*m/z*) 540.2 [M+H]⁺.

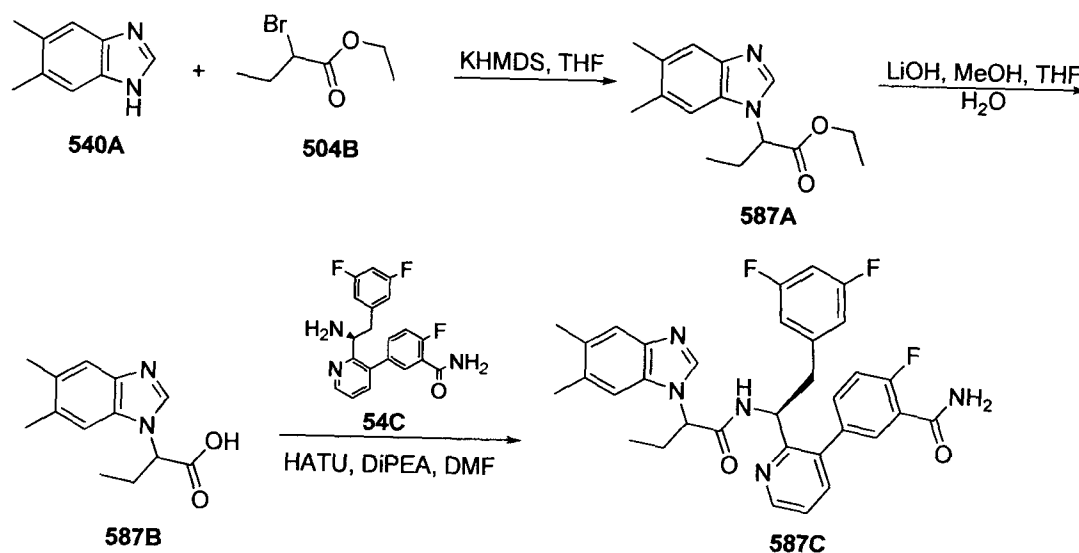
Example 585



Synthesis of (S)-5-(2-(1-(2-(5-chloro-1H-indol-1-yl)acetamido)-2-(3,5-difluorophenyl)ethyl)pyridin-3-yl)-2-fluorobenzamide (**585**):

The title compound was prepared according to the method presented in the synthesis of **56B** substituting 5-chloro-1H-indole for 1H-benzo[g]indole to provide the desired compound (24 mg, 61 %): ¹H NMR (400 MHz, dmso) δ 8.96 (d, 1H), 8.69 (d, 1H), 7.67 – 7.57 (m, 3H), 7.50 (s, 2H), 7.44 – 7.37 (m, 2H), 7.32 – 7.24 (m, 1H), 7.21 (d, 1H), 7.04 (d, 1H), 6.97 (d, 2H), 6.61 (d, 2H), 6.32 (d, 1H), 5.13 (s, 1H), 4.77 (s, 2H), 3.01 (d, 2H); MS (*m/z*) 563.9 [M+H]⁺.

Example 587



Synthesis of ethyl 2-(5,6-dimethyl-1H-benzo[d]imidazol-1-yl)butanoate (**587A**):

The title compound was prepared according to the method presented in Example 478

- 5 substituting **540A** for **478A** and **504B** for **478B** to provide the desired compound: MS (m/z) 261.3 $[\text{M}+\text{H}]^+$.

Synthesis of 2-(5,6-dimethyl-1H-benzo[d]imidazol-1-yl)butanoic acid (**587B**):

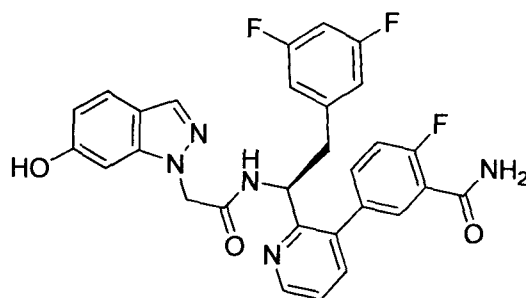
The title compound was prepared according to the method presented in Example 478

- 10 substituting ethyl 2-(5,6-dimethyl-1H-benzo[d]imidazol-1-yl)butanoate for **478C** to provide the desired compound: MS (m/z) 233.3 $[\text{M}+\text{H}]^+$.

Synthesis of 5-(2-((1S)-2-(3,5-difluorophenyl)-1-(2-(5,6-dimethyl-1H-benzo[d]imidazol-1-yl)butanamido)ethyl)pyridin-3-yl)-2-fluorobenzamide (**587C**):

- 15 The title compound was prepared according to the method presented in the synthesis of **54G** substituting 2-(5,6-dimethyl-1H-benzo[d]imidazol-1-yl)butanoic acid for **54F** to provide the desired compound (11 mg, 14 %): MS (m/z) 586.5 $[\text{M}+\text{H}]^+$.

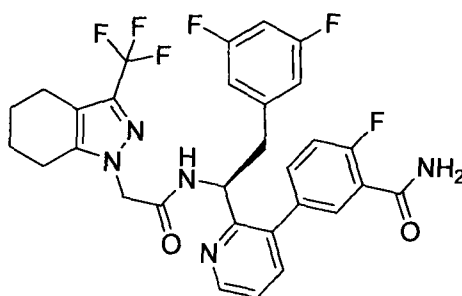
Example 588

**588**

Synthesis of (S)-5-(2-(2-(3,5-difluorophenyl)-1-(2-(6-hydroxy-1H-indazol-1-yl)acetamido)ethyl)pyridin-3-yl)-2-fluorobenzamide (**588**):

The title compound was prepared according to the method presented in Example **56** substituting 1H-indazol-6-ol for 1H-benzo[g]indole to provide the desired compound (10 mg, 16 %): ¹H NMR (400 MHz, dmso) δ 8.70 – 8.63 (m, 1H), 8.56 (d, 1H), 7.90 (s, 1H), 7.67 (d, 2H), 7.63 – 7.54 (m, 2H), 7.49 (d, 1H), 7.43 – 7.37 (m, 2H), 7.32 (dd, 1H), 6.85 (dd, 2H), 6.75 (dd, 1H), 6.49 (d, 2H), 5.22 (dd, 1H), 4.46 (d, 2H), 3.09 – 2.91 (m, 3H); MS (*m/z*) 546.2 [M+H]⁺.

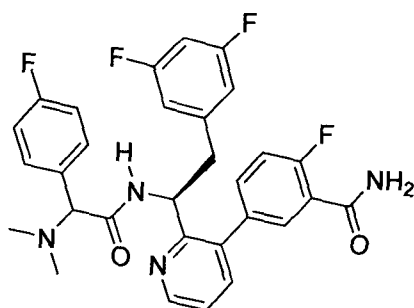
10 Example 589

**589**

Synthesis of (S)-5-(2-(2-(3,5-difluorophenyl)-1-(2-(3-(trifluoromethyl)-4,5,6,7-tetrahydro-1H-indazol-1-yl)acetamido)ethyl)pyridin-3-yl)-2-fluorobenzamide (**589**):

The title compound was prepared according to the method presented in the synthesis of **54G** utilizing **54B** and 2-(3-(trifluoromethyl)-4,5,6,7-tetrahydro-1H-indazol-1-yl)acetic acid to provide 40 mg of the desired compound in a 50 % yield: ¹H NMR (400 MHz, dmso) δ 8.92 (d, 1H), 8.67 (dd, 1H), 7.66 (s, 1H), 7.62 (dd, 1H), 7.49 (dd, 1H), 7.41 (dd, 2H), 7.36 – 7.25 (m, 1H), 6.92 (t, 1H), 6.57 (d, 2H), 5.17 (dd, 1H), 4.70 (s, 3H), 3.07 – 2.94 (m, 2H), 2.41 (s, 2H), 2.32 (d, 1H), 2.17 (d, 1H), 1.59 (d, 4H); MS (*m/z*) 603.3 [M+H]⁺.

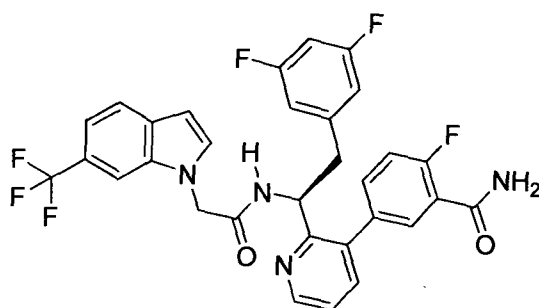
Example 590

**590**

Synthesis of 5-(2-((1S)-2-(3,5-difluorophenyl)-1-(2-(dimethylamino)-2-(4-fluorophenyl)acetamido)ethyl)pyridin-3-yl)-2-fluorobenzamide (**590**):

The title compound was prepared according to the method presented in the synthesis of **54G** substituting 2-(dimethylamino)-2-(4-fluorophenyl)acetic acid for **54F** to provide the desired compound (the second peak off HPLC, 4 mg, 6 %): ^1H NMR (400 MHz, dmsO) δ 10.15 – 10.06 (m, 1H), 9.58 (s, 1H), 8.68 (d, 1H), 7.77 – 7.66 (m, 2H), 7.63 (s, 1H), 7.50 (s, 1H), 7.48 – 7.36 (m, 2H), 7.36 – 7.28 (m, 2H), 7.18 (t, 2H), 6.78 (s, 1H), 6.35 (d, 2H), 5.20 (s, 1H), 4.78 (s, 1H), 2.91 (d, 2H), 2.58 (s, 3H), 2.33 (s, 3H); MS (m/z) 551.3 [$\text{M}+\text{H}$] $^+$.

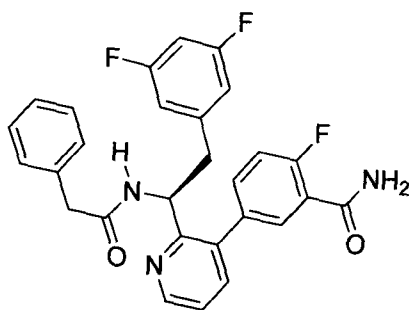
Example 591

**591**

Synthesis of (S)-5-(2-(2-(3,5-difluorophenyl)-1-(2-(6-(trifluoromethyl)-1H-indol-1-yl)acetamido)ethyl)pyridin-3-yl)-2-fluorobenzamide (**591**):

The title compound was prepared according to the method presented in Example **56** substituting 6-(trifluoromethyl)-1H-indole for 1H-benzo[g]indole to provide the desired compound (15 mg, 36%): ^1H NMR (400 MHz, dmsO) δ 9.02 (d, 1H), 8.67 (d, 1H), 7.67 (d, 1H), 7.61 (d, 2H), 7.58 (s, 2H), 7.45 (d, 1H), 7.40 (t, 3H), 7.24 (t, 2H), 6.86 (s, 1H), 6.54 (d, 2H), 6.49 (d, 1H), 5.13 (d, 1H), 4.89 (s, 2H), 3.00 (d, 2H); MS (m/z) 598.1 [$\text{M}+\text{H}$] $^+$.

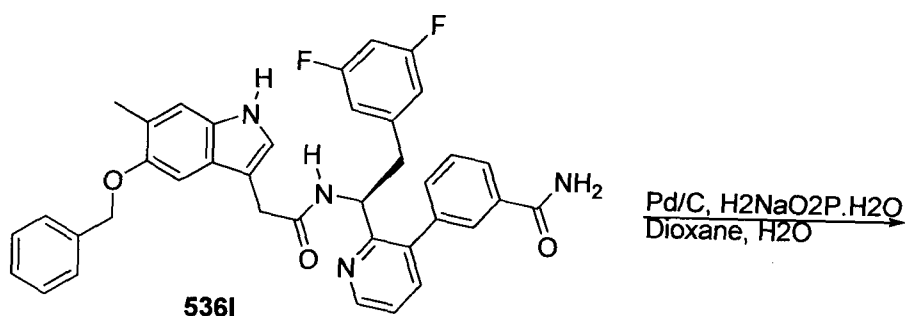
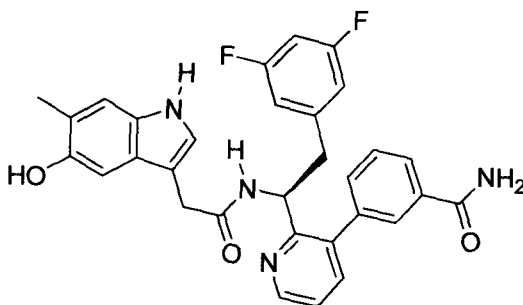
Example 592

**592**

Synthesis of (S)-5-(2-(2-(3,5-difluorophenyl)-1-(2-(5,6-dimethyl-1H-indol-1-yl)acetamido)ethyl)pyridin-3-yl)-2-fluorobenzamide (**592**):

The title compound was prepared according to the method presented in the synthesis of **54G** substituting 2-phenylacetic acid for **54F** to provide the desired compound (23 mg, 44 %): ^1H NMR (400 MHz, dmso) δ 8.73 (d, 1H), 8.66 (dd, 1H), 7.65 (d, 2H), 7.59 (dd, 1H), 7.50 (dd, 1H), 7.39 (dd, 2H), 7.34 – 7.24 (m, 1H), 7.14 (dq, 3H), 7.04 (d, 2H), 6.90 (t, 1H), 6.56 (d, 2H), 5.10 (dd, 1H), 3.34 (dd, 2H), 2.98 (d, 2H); MS (m/z) 490.6 $[\text{M}+\text{H}]^+$.

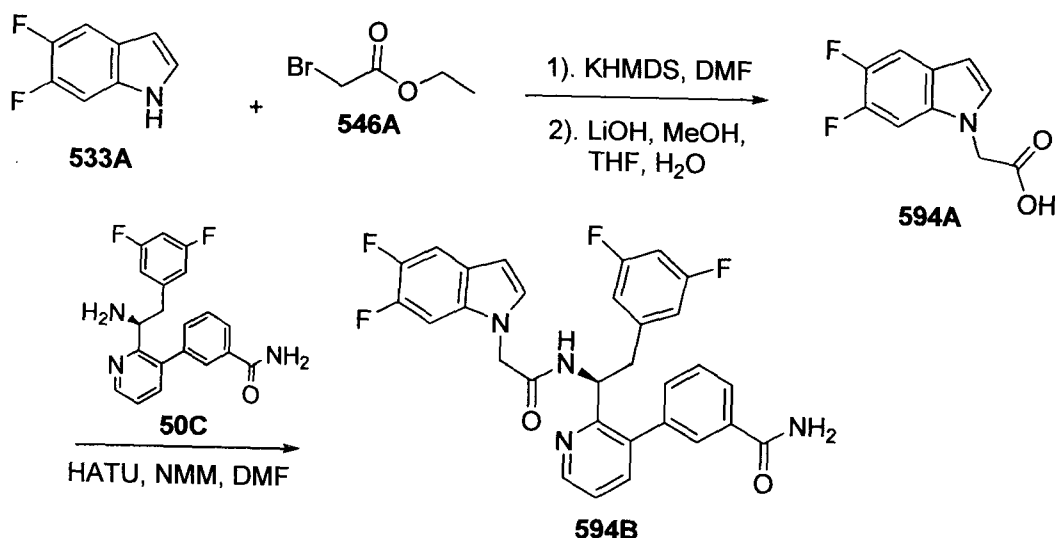
Example 593

**536I****593**

Synthesis of (S)-3-(2-(2-(3,5-difluorophenyl)-1-(2-(5-hydroxy-6-methyl-1H-indol-3-yl)acetamido)ethyl)pyridin-3-yl)benzamide (**593**):

A round bottom was charged with **536I** (30 mg, 0.05 mmol), dioxane (5 ml), Pd/C (10 mg), H₂NaO₂P•H₂O (60 mg, 0.6 mmol), and H₂O (1 ml). The resulting mixture was stirred at 95 °C until done as indicated by LC/MS. The reaction mixture was cooled to RT and filtered over a plug of celite, rinsing with ethyl acetate. The layers were partitioned and the organic layer was dried over sodium sulfate, filtered, concentrated and purified by HPLC to give the desired compound (16 mg, 66%): ¹H NMR (400 MHz, dmso) δ 10.32 (s, 1H), 8.66 – 8.57 (m, 1H), 8.35 (d, 1H), 7.96 (s, 1H), 7.86 (d, 1H), 7.69 (s, 1H), 7.58 (dd, 1H), 7.44 (t, 1H), 7.36 (dt, 3H), 6.95 (s, 1H), 6.90 – 6.80 (m, 2H), 6.76 (s, 1H), 6.37 (d, 2H), 5.27 – 5.16 (m, 1H), 3.37 (s, 2H), 2.91 (d, 2H), 2.14 (s, 3H); MS (*m/z*) 541.2 [M+H]⁺.

Example 594



15 Synthesis of ethyl 2-(5,6-difluoro-1H-indol-1-yl)acetate:

The title compound was prepared according to the method presented in Example 478 substituting ethyl 2-bromoacetate for **478B** and 5,6-difluoro-1H-indole for **478A** to provide the desired compound.

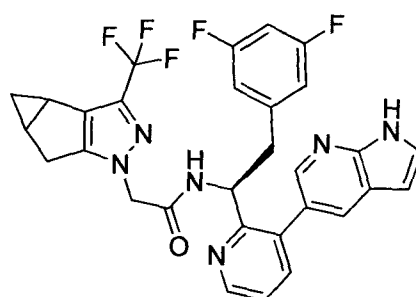
20 Synthesis of 2-(5,6-difluoro-1H-indol-1-yl)acetic acid (**594A**):

The title compound was prepared according to the method presented in Example 478 substituting ethyl 2-(5,6-difluoro-1H-indol-1-yl)acetate for **478C** to provide the desired compound: MS (*m/z*) 212.2 [M+H]⁺.

Synthesis of (S)-3-(2-(1-(2-(5,6-difluoro-1H-indol-1-yl)acetamido)-2-(3,5-difluorophenyl)ethyl)pyridin-3-yl)benzamide (**594B**):

The title compound was prepared according to the method presented in the synthesis of **50D** substituting 2-(5,6-difluoro-1H-indol-1-yl)acetic acid for 2-(5-fluoro-1H-indol-3-yl)acetic acid to provide the desired compound (27 mg, 44%): ¹H NMR (400 MHz, dmsO) δ 8.92 (d, 1H), 8.68 (d, 1H), 7.94 (s, 1H), 7.88 (d, 1H), 7.73 (s, 1H), 7.64 (d, 1H), 7.52 – 7.35 (m, 5H), 7.19 (d, 1H), 7.15 (dd, 1H), 6.88 (t, 1H), 6.52 (d, 2H), 6.34 (d, 1H), 5.18 (dd, 1H), 4.75 (s, 2H), 3.05 – 2.94 (m, 2H); MS (*m/z*) 547.6 [M+H]⁺.

10 Example 595



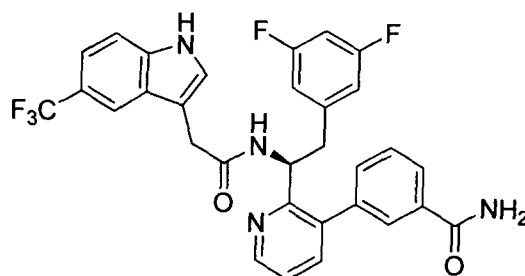
595

Synthesis of N-((S)-1-(3-(1H-pyrrolo[2,3-b]pyridin-5-yl)pyridin-2-yl)-2-(3,5-difluorophenyl)ethyl)-2-(3-(trifluoromethyl)-3b,4,4a,5-tetrahydro-1H-cyclopropa[3,4]cyclopenta[1,2-c]pyrazol-1-yl)acetamide (**595**):

The title compound was prepared according to the method presented in the synthesis of **61F** substituting **122E** for **61C** to provide the desired compound (18 mg, 17 %): ¹H NMR (400 MHz, cd₃od) δ 8.47 (d, 1H), 7.77 (s, 1H), 7.58 (s, 1H), 7.41 (d, 1H), 7.32 (d, 1H), 7.19 (dd, 1H), 6.44 (d, 1H), 6.38 (d, 1H), 6.01 (d, 2H), 5.15 – 5.02 (m, 1H), 4.49 – 4.41 (m, 2H), 2.82 (d, 3H), 2.55 (d, 1H), 2.41 (dd, 1H), 1.82 (s, 2H), 0.83 (d, 2H); MS (*m/z*) 579.4 [M+H]⁺.

20

Example 596



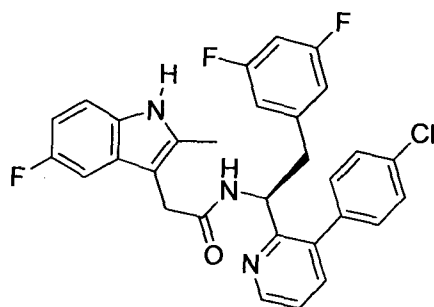
596

Synthesis of (S)-3-(2-(2-(3,5-difluorophenyl)-1-(2-(5-(trifluoromethyl)-1H-indol-3-yl)acetamido)ethyl)pyridin-3-yl)benzamide (**596**):

The title compound was prepared according to the method presented in the synthesis of **50D**

utilizing **50C** and **54F** to provide 23 mg of the desired compound in a 35% yield: ^1H NMR (400 MHz, dmsO) δ 11.24 (s, 1H), 8.69 (d, 1H), 8.63 (dd, 1H), 7.93 (s, 1H), 7.86 (d, 1H), 7.81 (s, 1H), 7.71 (s, 1H), 7.60 (dd, 1H), 7.48 – 7.34 (m, 4H), 7.28 (d, 1H), 7.20 (s, 1H), 6.82 (t, 1H), 6.43 (d, 2H), 5.19 (dd, 2H), 3.53 (s, 2H), 2.94 (d, 2H); MS (m/z) 579.2 $[\text{M}+\text{H}]^+$.

Example 597



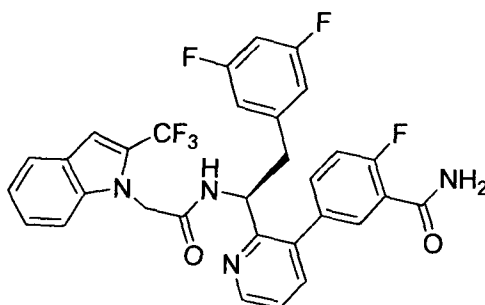
597

Synthesis of (S)-N-(1-(3-(4-chlorophenyl)pyridin-2-yl)-2-(3,5-difluorophenyl)ethyl)-2-(5-fluoro-2-methyl-1H-indol-3-yl)acetamide (**597**):

The title compound was prepared according to the method presented in the synthesis of **36F**

utilizing **36E** and **517D** to provide 13 mg of the desired compound in a 21 % yield: ^1H NMR (400 MHz, dmsO) δ 10.76 (s, 1H), 8.63 (dd, 1H), 8.59 (d, 1H), 7.53 (dd, 1H), 7.44 – 7.32 (m, 3H), 7.23 (d, 2H), 7.11 (dd, 1H), 7.06 (dd, 1H), 6.91 (t, 1H), 6.71 (td, 1H), 6.42 (d, 2H), 5.11 (dd, 1H), 3.45 – 3.29 (m, 2H), 3.00 – 2.82 (m, 2H), 2.20 (s, 3H); MS (m/z) 534.6 $[\text{M}+\text{H}]^+$.

Example 599

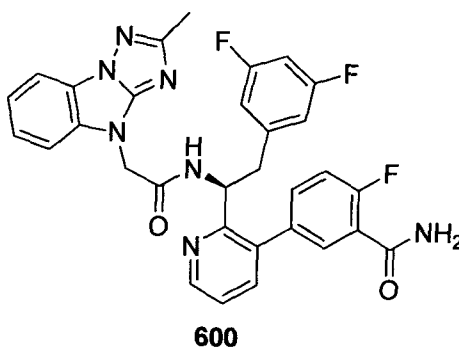


599

Synthesis of (S)-5-(2-(2-(3,5-difluorophenyl)-1-(2-(2-(trifluoromethyl)-1H-indol-1-yl)acetamido)ethyl)pyridin-3-yl)-2-fluorobenzamide (**599**):

The title compound was prepared according to the method presented in Example 56 substituting 2-(trifluoromethyl)-1H-indole for 1H-benzo[g]indole to provide the desired compound (14 mg, 34%): ¹H NMR (400 MHz, dmso) δ 8.97 (d, 1H), 8.70 (d, 1H), 7.60 (dd, 4H), 7.49 – 7.36 (m, 3H), 7.30 – 7.18 (m, 3H), 7.10 (t, 1H), 7.01 (s, 1H), 6.94 (s, 1H), 6.58 (d, 2H), 5.13 (d, 1H), 4.88 (s, 2H), 3.00 (d, 2H); MS (*m/z*) 597.5 [M+H]⁺.

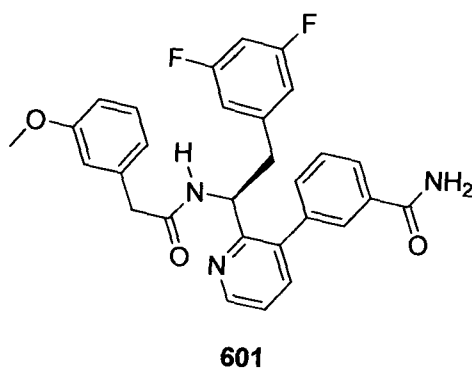
Example 600



Synthesis of (S)-5-(2-(2-(3,5-difluorophenyl)-1-(2-(2-methyl-4H-benzo[4,5]imidazo[1,2-b][1,2,4]triazol-4-yl)acetamido)ethyl)pyridin-3-yl)-2-fluorobenzamide (**600**):

The title compound was prepared according to the method presented in the synthesis of **54G** substituting 2-(2-methyl-4H-benzimidazo[1,2-b][1,2,4]triazol-4-yl)acetic acid. for **54F** to provide the desired compound (12 mg, 25 %): ¹H NMR (400 MHz, dmso) δ 9.11 (d, 1H), 8.70 (d, 1H), 7.63 (dd, 4H), 7.49 – 7.35 (m, 3H), 7.29 – 7.18 (m, 4H), 6.94 (s, 1H), 6.58 (d, 2H), 5.15 (d, 1H), 4.82 (s, 2H), 3.03 (d, 2H), 2.32 (s, 3H); MS (*m/z*) 584.6 [M+H]⁺.

Example 601



Synthesis of (S)-3-(2-(2-(3,5-difluorophenyl)-1-(2-(3-methoxyphenyl)acetamido)ethyl)pyridin-3-yl)benzamide (**601**):

The title compound was prepared according to the method presented in the synthesis of **50D** utilizing **50C** and 2-(3-methoxyphenyl)acetic acid to provide 18 mg of the desired compound in

a 40 % yield: ^1H NMR (400 MHz, dmso) δ 8.71 (d, 1H), 8.66 (d, 1H), 7.94 (s, 1H), 7.88 (d, 1H), 7.75 (s, 1H), 7.62 (dd, 1H), 7.47 (t, 1H), 7.44 – 7.37 (m, 3H), 7.06 (t, 1H), 6.88 (t, 1H), 6.68 (d, 1H), 6.65 (s, 1H), 6.61 (d, 1H), 6.48 (d, 2H), 5.16 (d, 1H), 3.64 (s, 3H), 3.32 (dd, 2H), 2.95 (d, 2H); MS (m/z) 502.2 $[\text{M}+\text{H}]^+$.

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Example 602. The following illustrate representative pharmaceutical dosage forms, containing a compound of formula I ('Compound X'), for therapeutic or prophylactic use in humans.

10	(i) <u>Tablet 1</u>	<u>mg/tablet</u>
	Compound X=	100.0
	Lactose	77.5
	Povidone	15.0
	Croscarmellose sodium	12.0
15	Microcrystalline cellulose	92.5
	Magnesium stearate	<u>3.0</u>
		300.0
	(ii) <u>Tablet 2</u>	<u>mg/tablet</u>
20	Compound X=	20.0
	Microcrystalline cellulose	410.0
	Starch	50.0
	Sodium starch glycolate	15.0
	Magnesium stearate	<u>5.0</u>
25		500.0
	(iii) <u>Capsule</u>	<u>mg/capsule</u>
	Compound X=	10.0
	Colloidal silicon dioxide	1.5
	Lactose	465.5
30	Pregelatinized starch	120.0
	Magnesium stearate	<u>3.0</u>
		600.0
	(iv) <u>Injection 1 (1 mg/ml)</u>	<u>mg/ml</u>
35	Compound X= (free acid form)	1.0
	Dibasic sodium phosphate	12.0
	Monobasic sodium phosphate	0.7
	Sodium chloride	4.5
	1.0 N Sodium hydroxide solution	
40	(pH adjustment to 7.0-7.5)	q.s.
	Water for injection	q.s. ad 1 mL

	(v) <u>Injection 2 (10 mg/ml)</u>	<u>mg/ml</u>
	Compound X= (free acid form)	10.0
	Monobasic sodium phosphate	0.3
	Dibasic sodium phosphate	1.1
5	Polyethylene glycol 400	200.0
	1.0 N Sodium hydroxide solution (pH adjustment to 7.0-7.5)	q.s.
	Water for injection	q.s. ad 1 mL
10	(vi) <u>Aerosol</u>	<u>mg/can</u>
	Compound X=	20.0
	Oleic acid	10.0
	Trichloromonofluoromethane	5,000.0
	Dichlorodifluoromethane	10,000.0
15	Dichlorotetrafluoroethane	5,000.0

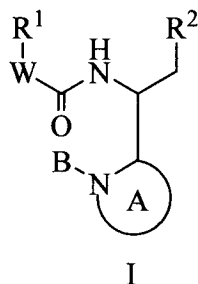
The above formulations may be obtained by conventional procedures well known in the pharmaceutical art.

- 20 All 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.

CLAIMS

What is claimed is:

1. A compound of formula I:



wherein:

A is a 6-membered heteroaryl comprising one or two nitrogens, wherein the 6-membered heteroaryl is substituted with one Z^1 group and optionally substituted with one or more Z^2 groups;

B is absent; or B is $-O^-$ and the nitrogen to which the $-O^-$ group is attached is N^+ ;

W is $-CR^{3a}R^{3b}-$, $-O-$, $-NR^4-$, $-OCR^{3a}R^{3b}-$ or absent;

R^1 is aryl, heteroaryl or heterocycle, wherein any aryl, heteroaryl or heterocycle of R^1 is optionally substituted with one or more Z^3 groups;

R^2 is a 6-membered aryl, 5-membered heteroaryl or 6-membered heteroaryl, wherein any 6-membered aryl, 5-membered heteroaryl or 6-membered heteroaryl of R^2 is optionally substituted with one or more Z^4 groups;

each R^{3a} and R^{3b} is independently selected from H, halogen, (C_1-C_6) alkyl, (C_3-C_7) carbocycle, (C_1-C_3) haloalkyl, (C_1-C_6) heteroalkyl, heteroaryl (C_1-C_6) alkyl-, heterocyclyl (C_1-C_6) alkyl-, $-NR_aR_b$, and $-NR_cCOR_d$, wherein any (C_1-C_6) alkyl of R^{3a} and R^{3b} is optionally substituted with one or more OH groups; or R^{3a} and R^{3b} together with the carbon to which they are attached form a (C_3-C_6) carbocycle;

R^4 is selected from H, (C_1-C_6) alkyl, (C_3-C_6) carbocycle, aryl (C_1-C_6) alkyl- and heteroaryl (C_1-C_6) alkyl-;

R_a and R_b 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, aryl, haloaryl, haloheteroaryl, haloheterocycle, (C_1-C_8) haloalkyl and (C_1-C_8) heteroalkyl, or R_a and R_b together with the nitrogen to which they are attached form a 5, 6 or 7-membered heterocycle;

each R_c 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-C_8) haloalkyl and (C_1-C_8) heteroalkyl;

each R_d is independently selected from (C₁-C₈)alkyl, (C₂-C₈)alkenyl, (C₂-C₈)alkynyl, (C₃-C₇)carbocycle, heterocycle, heteroaryl, aryl, haloaryl, haloheteroaryl, haloheterocycle, (C₁-C₈)haloalkyl and (C₁-C₈)heteroalkyl;

each Z^1 is independently selected from (C₂-C₈)alkyl, (C₂-C₈)alkenyl, (C₂-C₈)alkynyl, (C₃-C₇)carbocycle, aryl, heteroaryl, heterocycle and -OR_{n1}, wherein any (C₃-C₇)carbocycle, aryl, heteroaryl and heterocycle of Z^1 is optionally substituted with one or more Z^{1a} or Z^{1b} groups and wherein any (C₁-C₈)alkyl, (C₂-C₈)alkenyl and (C₂-C₈)alkynyl of Z^1 is optionally substituted with one or more Z^{1a} groups;

each Z^{1a} is independently selected from (C₃-C₇)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)₂OH, -S(O)₂R_{p2}, -S(O)₂NR_{q2}R_{r2}, -NR_{q2}R_{r2}, -NR_{n2}COR_{p2}, -NR_{n2}CO₂R_{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}, NO₂, -C(O)R_{n2}, -C(O)OR_{n2}, -C(O)NR_{q2}R_{r2} and -S(O)₂NR_{n2}COR_{p2}, wherein any (C₃-C₇)carbocycle, aryl, heteroaryl and heterocycle of Z^{1a} is optionally substituted with one or more Z^{1c} or Z^{1d} groups;

each Z^{1b} is independently selected from (C₁-C₈)alkyl, (C₂-C₈)alkenyl and (C₂-C₈)alkynyl, wherein any (C₁-C₈)alkyl, (C₂-C₈)alkenyl and (C₂-C₈)alkynyl of Z^{1b} is optionally substituted with one or more Z^{1c} groups;

each Z^{1c} is independently selected from (C₃-C₇)carbocycle, aryl, heteroaryl, heterocycle, halogen, -CN, -OR_{n3}, -OC(O)R_{p3}, -OC(O)NR_{q3}R_{r3}, -SR_{n3}, -S(O)R_{p3}, -S(O)₂OH, -S(O)₂R_{p3}, -S(O)₂NR_{q3}R_{r3}, -NR_{q3}R_{r3}, -NR_{n3}COR_{p3}, -NR_{n3}CO₂R_{p3}, -NR_{n3}CONR_{q3}R_{r3}, -NR_{n3}S(O)₂R_{p3}, -NR_{n3}S(O)₂OR_{p3}, -NR_{n3}S(O)₂NR_{q3}R_{r3}, NO₂, -C(O)R_{n3}, -C(O)OR_{n3}, -C(O)NR_{q3}R_{r3}, haloaryl, haloheteroaryl, haloheterocycle and (C₁-C₈)heteroalkyl;

each Z^{1d} is independently selected from (C₁-C₈)alkyl, (C₂-C₈)alkenyl, (C₂-C₈)alkynyl and (C₁-C₈)haloalkyl;

each R_{n1} is independently selected from (C₁-C₈)alkyl, (C₂-C₈)alkenyl, (C₂-C₈)alkynyl, (C₃-C₇)carbocycle, heterocycle, heteroaryl and aryl, wherein any (C₃-C₇)carbocycle, aryl, heteroaryl and heterocycle of R_{n1} is optionally substituted with one or more Z^{1a} or Z^{1b} groups, and wherein any (C₁-C₈)alkyl, (C₂-C₈)alkenyl and (C₂-C₈)alkynyl of R_{n1} is optionally substituted with one or more Z^{1a} groups;

each R_{n2} is independently selected from H, (C₁-C₈)alkyl, (C₂-C₈)alkenyl, (C₂-C₈)alkynyl, (C₃-C₇)carbocycle, heterocycle, heteroaryl and aryl, wherein any (C₃-C₇)carbocycle, aryl, heteroaryl and heterocycle of R_{n2} is optionally substituted with one or more Z^{1c} or Z^{1d} groups, and wherein any (C₁-C₈)alkyl, (C₂-C₈)alkenyl and (C₂-C₈)alkynyl of R_{n2} is optionally substituted with one or more Z^{1c} groups;

each R_{p2} is independently selected from (C₁-C₈)alkyl, (C₂-C₈)alkenyl, (C₂-C₈)alkynyl, (C₃-C₇)carbocycle, heterocycle, heteroaryl and aryl, wherein any (C₃-C₇)carbocycle, aryl, heteroaryl and heterocycle of R_{p2} is optionally substituted with one or more Z^{1c} or Z^{1d} groups, and wherein any (C₁-C₈)alkyl, (C₂-C₈)alkenyl and (C₂-C₈)alkynyl of R_{p2} is optionally substituted with one or more Z^{1c} groups;

R_{q2} and R_{r2} are each independently selected from H, (C₁-C₈)alkyl, (C₂-C₈)alkenyl, (C₂-C₈)alkynyl, (C₃-C₇)carbocycle, heterocycle, heteroaryl and aryl, wherein any (C₃-C₇)carbocycle, aryl, heteroaryl and heterocycle of R_{q2} or R_{r2} is optionally substituted with one or Z^{1c} or Z^{1d} groups, and wherein any (C₁-C₈)alkyl, (C₂-C₈)alkenyl and (C₂-C₈)alkynyl of R_{q2} or R_{r2} is optionally substituted with one or more Z^{1c} groups, or R_{q2} and R_{r2} 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 Z^{1c} or Z^{1d} groups;

each R_{n3} is independently selected from H, (C₁-C₈)alkyl, (C₂-C₈)alkenyl, (C₂-C₈)alkynyl, (C₃-C₇)carbocycle, heterocycle, heteroaryl, aryl, haloaryl, haloheteroaryl, haloheterocycle, (C₁-C₈)haloalkyl and (C₁-C₈)heteroalkyl;

each R_{p3} is independently selected from (C₁-C₈)alkyl, (C₂-C₈)alkenyl, (C₂-C₈)alkynyl, (C₃-C₇)carbocycle, heterocycle, heteroaryl, aryl, haloaryl, haloheteroaryl, haloheterocycle, (C₁-C₈)haloalkyl and (C₁-C₈)heteroalkyl;

R_{q3} and R_{r3} are each independently selected from H, (C₁-C₈)alkyl, (C₂-C₈)alkenyl, (C₂-C₈)alkynyl, (C₃-C₇)carbocycle, heterocycle, heteroaryl, aryl, haloaryl, haloheteroaryl, haloheterocycle, (C₁-C₈)haloalkyl and (C₁-C₈)heteroalkyl, or R_{q3} and R_{r3} together with the nitrogen to which they are attached form a 5, 6 or 7-membered heterocycle;

each Z^2 is independently selected from (C₁-C₆)alkyl, (C₁-C₆)haloalkyl, (C₃-C₇)carbocycle, halogen, CN, OH and -O(C₁-C₆)alkyl;

each Z^3 is independently selected from (C₁-C₈)alkyl, (C₂-C₈)alkenyl, (C₂-C₈)alkynyl, (C₃-C₇)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)₂OH, -S(O)₂R_{p4}, -S(O)₂NR_{q4}R_{r4}, -NR_{q4}R_{r4}, -NR_{n4}COR_{p4}, -NR_{n4}CO₂R_{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}, NO₂, -C(O)R_{n4}, -C(O)OR_{n4}, -C(O)NR_{q4}R_{r4} and -B(OR_{q4})(OR_{r4}) wherein any (C₃-C₇)carbocycle, aryl, heteroaryl and heterocycle of Z^3 is optionally substituted with one or more Z^{3a} or Z^{3b} groups, and wherein any (C₁-C₈)alkyl, (C₂-C₈)alkenyl and (C₂-C₈)alkynyl of Z^3 is optionally substituted with one or more Z^{3a} groups;

each Z^{3a} is independently selected from (C₃-C₇)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)₂OH, -S(O)₂R_{p5}, -S(O)₂NR_{q5}R_{r5}, -NR_{q5}R_{r5}, -NR_{n5}COR_{p5}, -NR_{n5}CO₂R_{p5}, -NR_{n5}CONR_{q5}R_{r5}, -NR_{n5}S(O)₂R_{p5},

$-\text{NR}_{\text{n}5}\text{S}(\text{O})_2\text{OR}_{\text{p}5}$, $-\text{NR}_{\text{n}5}\text{S}(\text{O})_2\text{NR}_{\text{q}5}\text{R}_{\text{r}5}$, NO_2 , $-\text{C}(\text{O})\text{R}_{\text{n}5}$, $-\text{C}(\text{O})\text{OR}_{\text{n}5}$, and $-\text{C}(\text{O})\text{NR}_{\text{q}5}\text{R}_{\text{r}5}$, wherein any (C₃-C₇)carbocycle, aryl, heteroaryl and heterocycle of $\text{Z}^{3\text{a}}$ is optionally substituted with one or more $\text{Z}^{3\text{c}}$ or $\text{Z}^{3\text{d}}$ groups;

each $\text{Z}^{3\text{b}}$ is independently selected from (C₁-C₈)alkyl, (C₂-C₈)alkenyl and (C₂-C₈)alkynyl, wherein any (C₁-C₈)alkyl, (C₂-C₈)alkenyl and (C₂-C₈)alkynyl of $\text{Z}^{3\text{b}}$ is optionally substituted with one or more $\text{Z}^{3\text{c}}$ groups;

each $\text{Z}^{3\text{c}}$ is independently selected from (C₃-C₇)carbocycle, aryl, heteroaryl, heterocycle, halogen, -CN, $-\text{OR}_{\text{n}6}$, $-\text{OC}(\text{O})\text{R}_{\text{p}6}$, $-\text{OC}(\text{O})\text{NR}_{\text{q}6}\text{R}_{\text{r}6}$, $-\text{SR}_{\text{n}6}$, $-\text{S}(\text{O})\text{R}_{\text{p}6}$, $-\text{S}(\text{O})_2\text{OH}$, $-\text{S}(\text{O})_2\text{R}_{\text{p}6}$, $-\text{S}(\text{O})_2\text{NR}_{\text{q}6}\text{R}_{\text{r}6}$, $-\text{NR}_{\text{q}6}\text{R}_{\text{r}6}$, $-\text{NR}_{\text{n}6}\text{COR}_{\text{p}6}$, $-\text{NR}_{\text{n}6}\text{CO}_2\text{R}_{\text{p}6}$, $-\text{NR}_{\text{n}6}\text{CONR}_{\text{q}6}\text{R}_{\text{r}6}$, $-\text{NR}_{\text{n}6}\text{S}(\text{O})_2\text{R}_{\text{p}6}$, $-\text{NR}_{\text{n}6}\text{S}(\text{O})_2\text{OR}_{\text{p}6}$, $-\text{NR}_{\text{n}6}\text{S}(\text{O})_2\text{NR}_{\text{q}6}\text{R}_{\text{r}6}$, NO_2 , $-\text{C}(\text{O})\text{R}_{\text{n}6}$, $-\text{C}(\text{O})\text{OR}_{\text{n}6}$, $-\text{C}(\text{O})\text{NR}_{\text{q}6}\text{R}_{\text{r}6}$, haloaryl, haloheteroaryl, haloheterocycle and (C₁-C₈)heteroalkyl;

each $\text{Z}^{3\text{d}}$ is independently selected from (C₁-C₈)alkyl, (C₂-C₈)alkenyl, (C₂-C₈)alkynyl, and (C₁-C₈)haloalkyl;

each $\text{R}_{\text{n}4}$ is independently selected from H, (C₁-C₈)alkyl, (C₂-C₈)alkenyl, (C₂-C₈)alkynyl, (C₃-C₇)carbocycle, heterocycle, heteroaryl and aryl, wherein any (C₃-C₇)carbocycle, aryl, heteroaryl and heterocycle of $\text{R}_{\text{n}4}$ is optionally substituted with one or more $\text{Z}^{3\text{a}}$ or $\text{Z}^{3\text{b}}$ groups, and wherein any (C₁-C₈)alkyl, (C₂-C₈)alkenyl and (C₂-C₈)alkynyl of $\text{R}_{\text{n}4}$ is optionally substituted with one or more $\text{Z}^{3\text{a}}$ groups;

each $\text{R}_{\text{p}4}$ is independently selected from (C₁-C₈)alkyl, (C₂-C₈)alkenyl, (C₂-C₈)alkynyl, (C₃-C₇)carbocycle, heterocycle, heteroaryl and aryl, wherein any (C₃-C₇)carbocycle, aryl, heteroaryl, or heterocycle of $\text{R}_{\text{p}4}$ is optionally substituted with one or more $\text{Z}^{3\text{a}}$ or $\text{Z}^{3\text{b}}$ groups, and wherein any (C₁-C₈)alkyl, (C₂-C₈)alkenyl or (C₂-C₈)alkynyl of $\text{R}_{\text{p}4}$ is optionally substituted with one or more $\text{Z}^{3\text{a}}$ groups;

$\text{R}_{\text{q}4}$ and $\text{R}_{\text{r}4}$ are each independently selected from H, (C₁-C₈)alkyl, (C₂-C₈)alkenyl, (C₂-C₈)alkynyl, (C₃-C₇)carbocycle, heterocycle, heteroaryl and aryl, wherein any (C₃-C₇)carbocycle, aryl, heteroaryl and heterocycle of $\text{R}_{\text{q}4}$ or $\text{R}_{\text{r}4}$ is optionally substituted with one or more $\text{Z}^{3\text{a}}$ or $\text{Z}^{3\text{b}}$ groups, and wherein any (C₁-C₈)alkyl, (C₂-C₈)alkenyl and (C₂-C₈)alkynyl of $\text{R}_{\text{q}4}$ or $\text{R}_{\text{r}4}$ is optionally substituted with one or more $\text{Z}^{3\text{a}}$ groups, or $\text{R}_{\text{q}4}$ and $\text{R}_{\text{r}4}$ 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 $\text{Z}^{3\text{a}}$ or $\text{Z}^{3\text{b}}$ groups;

each $\text{R}_{\text{n}5}$ is independently selected from H, (C₁-C₈)alkyl, (C₂-C₈)alkenyl, (C₂-C₈)alkynyl, (C₃-C₇)carbocycle, heterocycle, heteroaryl and aryl, wherein any (C₃-C₇)carbocycle, aryl, heteroaryl and heterocycle of $\text{R}_{\text{n}5}$ is optionally substituted with one or more $\text{Z}^{3\text{c}}$ or $\text{Z}^{3\text{d}}$ groups, and wherein any (C₁-C₈)alkyl, (C₂-C₈)alkenyl and (C₂-C₈)alkynyl of $\text{R}_{\text{n}5}$ is optionally substituted with one or more $\text{Z}^{3\text{c}}$ groups;

each R_{p5} is independently selected from (C₁-C₈)alkyl, (C₂-C₈)alkenyl, (C₂-C₈)alkynyl, (C₃-C₇)carbocycle, heterocycle, heteroaryl and aryl, wherein any (C₃-C₇)carbocycle, aryl, heteroaryl and heterocycle of R_{p5} is optionally substituted with one or more Z^{3c} or Z^{3d} groups, and wherein any (C₁-C₈)alkyl, (C₂-C₈)alkenyl and (C₂-C₈)alkynyl of R_{p5} is optionally substituted with one or more Z^{3c} groups;

R_{q5} and R_{r5} are each independently selected from H, (C₁-C₈)alkyl, (C₂-C₈)alkenyl, (C₂-C₈)alkynyl, (C₃-C₇)carbocycle, heterocycle, heteroaryl and aryl, wherein any (C₃-C₇)carbocycle, aryl, heteroaryl and heterocycle of R_{q5} or R_{r5} is optionally substituted with one or more Z^{3c} or Z^{3d} groups, and wherein any (C₁-C₈)alkyl, (C₂-C₈)alkenyl and (C₂-C₈)alkynyl of R_{q5} or R_{r5} is optionally substituted with one or more Z^{3c} 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 Z^{3c} or Z^{3d} groups;

each R_{n6} is independently selected from H, (C₁-C₈)alkyl, (C₂-C₈)alkenyl, (C₂-C₈)alkynyl, (C₃-C₇)carbocycle, heterocycle, heteroaryl, aryl, haloaryl, haloheteroaryl, haloheterocycle, (C₁-C₈)haloalkyl and (C₁-C₈)heteroalkyl;

each R_{p6} is independently selected from (C₁-C₈)alkyl, (C₂-C₈)alkenyl, (C₂-C₈)alkynyl, (C₃-C₇)carbocycle, heterocycle, heteroaryl, aryl, haloaryl, haloheteroaryl, haloheterocycle, (C₁-C₈)haloalkyl and (C₁-C₈)heteroalkyl;

R_{q6} and R_{r6} are each independently selected from H, (C₁-C₈)alkyl, (C₂-C₈)alkenyl, (C₂-C₈)alkynyl, (C₃-C₇)carbocycle, heterocycle, heteroaryl, aryl, haloaryl, haloheteroaryl, haloheterocycle, (C₁-C₈)haloalkyl and (C₁-C₈)heteroalkyl, or R_{q6} and R_{r6} together with the nitrogen to which they are attached form a 5, 6 or 7-membered heterocycle;

each Z^4 is independently selected from (C₁-C₈)alkyl, (C₂-C₈)alkenyl, (C₂-C₈)alkynyl, (C₃-C₇)carbocycle, aryl, heteroaryl, heterocycle, halogen, -CN, -OR_{n8}, -OC(O)R_{p8}, -OC(O)NR_{q8}R_{r8}, -SR_{n8}, -S(O)R_{p8}, -S(O)₂OH, -S(O)₂R_{p8}, -S(O)₂NR_{q8}R_{r8}, -NR_{q8}R_{r8}, -NR_{n8}COR_{p8}, -NR_{n8}CO₂R_{p8}, -NR_{n8}CONR_{q8}R_{r8}, -NR_{n8}S(O)₂R_{p8}, -NR_{n8}S(O)₂OR_{p8}, -NR_{n8}S(O)₂NR_{q8}R_{r8}, NO₂, -C(O)R_{n8}, -C(O)OR_{n8}, and -C(O)NR_{q8}R_{r8}, wherein any (C₃-C₇)carbocycle, aryl, heteroaryl and heterocycle of Z^4 is optionally substituted with one or more Z^{4c} or Z^{4d} groups and wherein any (C₁-C₈)alkyl, (C₂-C₈)alkenyl and (C₂-C₈)alkynyl of Z^4 is optionally substituted with one or more Z^{4c} groups;

each Z^{4c} is independently selected from (C₃-C₇)carbocycle, aryl, heteroaryl, heterocycle, halogen, -CN, -OR_{n9}, -OC(O)R_{p9}, -OC(O)NR_{q9}R_{r9}, -SR_{n9}, -S(O)R_{p9}, -S(O)₂OH, -S(O)₂R_{p9}, -S(O)₂NR_{q9}R_{r9}, -NR_{q9}R_{r9}, -NR_{n9}COR_{p9}, -NR_{n9}CO₂R_{p9}, -NR_{n9}CONR_{q9}R_{r9}, -NR_{n9}S(O)₂R_{p9}, -NR_{n9}S(O)₂OR_{p9}, -NR_{n9}S(O)₂NR_{q9}R_{r9}, NO₂, -C(O)R_{n9}, -C(O)OR_{n9}, -C(O)NR_{q9}R_{r9}, haloaryl, haloheteroaryl, haloheterocycle and (C₁-C₈)heteroalkyl;

each Z^{4d} is independently selected from of (C₁-C₈)alkyl, (C₂-C₈)alkenyl, (C₂-C₈)alkynyl and (C₁-C₈)haloalkyl;

each R_{n8} is independently selected from H, (C₁-C₈)alkyl, (C₂-C₈)alkenyl, (C₂-C₈)alkynyl, (C₃-C₇)carbocycle, heterocycle, heteroaryl and aryl, wherein any (C₃-C₇)carbocycle, aryl, heteroaryl and heterocycle of R_{n8} is optionally substituted with one or more Z^{4c} or Z^{4d} groups, and wherein any (C₁-C₈)alkyl, (C₂-C₈)alkenyl or (C₂-C₈)alkynyl of R_{n8} is optionally substituted with one or more Z^{4c} groups;

each R_{p8} is independently selected from (C₁-C₈)alkyl, (C₁-C₆)haloalkyl, (C₂-C₈)alkenyl, (C₂-C₈)alkynyl, (C₃-C₇)carbocycle, heterocycle, heteroaryl and aryl, wherein any (C₃-C₇)carbocycle, aryl, heteroaryl and heterocycle of R_{p8} is optionally substituted with one or more Z^{4c} or Z^{4d} groups, and wherein any (C₁-C₈)alkyl, (C₂-C₈)alkenyl and (C₂-C₈)alkynyl of R_{p8} is optionally substituted with one or more Z^{4c} groups;

R_{q8} and R_{r8} are each independently selected from H, (C₁-C₈)alkyl, (C₂-C₈)alkenyl, (C₂-C₈)alkynyl, (C₃-C₇)carbocycle, heterocycle, heteroaryl and aryl, wherein any (C₃-C₇)carbocycle, aryl, heteroaryl and heterocycle of R_{q8} or R_{r8} is optionally substituted with one or more Z^{4c} or Z^{4d} groups, and wherein any (C₁-C₈)alkyl, (C₂-C₈)alkenyl and (C₂-C₈)alkynyl of R_{q8} or R_{r8} is optionally substituted with one or more Z^{4c} groups, or R_{q8} and R_{r8} 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 Z^{4c} or Z^{4d} groups;

each R_{n9} is independently selected from H, (C₁-C₈)alkyl, (C₂-C₈)alkenyl, (C₂-C₈)alkynyl, (C₃-C₇)carbocycle, heterocycle, heteroaryl, aryl, haloaryl, haloheteroaryl, haloheterocycle, (C₁-C₈)haloalkyl and (C₁-C₈)heteroalkyl;

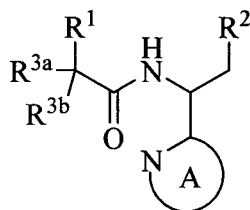
each R_{p9} is independently selected from (C₁-C₈)alkyl, (C₂-C₈)alkenyl, (C₂-C₈)alkynyl, (C₃-C₇)carbocycle, heterocycle, heteroaryl, aryl, haloaryl, haloheteroaryl, haloheterocycle, (C₁-C₈)haloalkyl and (C₁-C₈)heteroalkyl; and

R_{q9} and R_{r9} are each independently selected from H, (C₁-C₈)alkyl, (C₂-C₈)alkenyl, (C₂-C₈)alkynyl, (C₃-C₇)carbocycle, heterocycle, heteroaryl, aryl, haloaryl, haloheteroaryl, haloheterocycle, (C₁-C₈)haloalkyl and (C₁-C₈)heteroalkyl; or R_{q9} and R_{r9} together with the nitrogen to which they are attached form a 5, 6 or 7-membered heterocycle;

or a salt thereof.

2. The compound of claim 1 wherein W is -CR^{3a}R^{3b}-, -OCR^{3a}R^{3b}- or absent.
3. The compound of claim 1 wherein W is -CR^{3a}R^{3b}-.

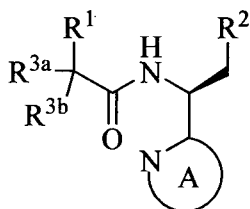
4. The compound of any one of claims 1-3 wherein B is absent.
5. The compound of claim 1 which is a compound of formula Ibb:



Ibb

or a salt thereof.

6. The compound of claim 1 which is a compound of formula Icc:

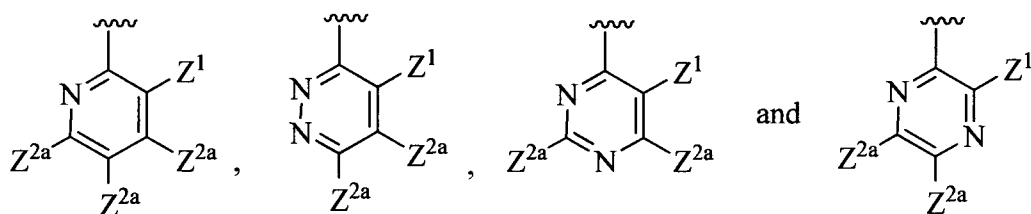


Icc

or a salt thereof.

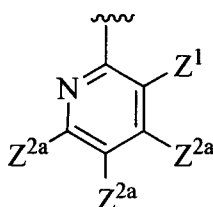
7. The compound of any one of claims 1-6 wherein each R^{3a} and R^{3b} is independently selected from H, (C₁-C₆)alkyl, (C₃-C₇)carbocycle, (C₁-C₃)haloalkyl and -NR_aR_b, wherein any (C₁-C₆)alkyl of R^{3a} and R^{3b} is optionally substituted with one or more OH groups; or R^{3a} and R^{3b} together with the carbon to which they are attached form a (C₃-C₆)carbocycle.
8. The compound of any one of claims 1-6 wherein each R^{3a} and R^{3b} is independently selected from H, (C₁-C₆)alkyl, (C₁-C₆)heteroalkyl, (C₁-C₃)haloalkyl and heterocyclyl(C₁-C₆)alkyl-.
9. The compound of any one of claims 1-6 wherein each R^{3a} and R^{3b} is H.
10. The compound of any one of claims 1-9 wherein A is pyridinyl, pyrimidinyl, pyrazinyl or pyridazinyl, wherein any pyridinyl, pyrimidinyl, pyrazinyl, or pyridazinyl of A is substituted with one Z¹ group and optionally substituted with one or more Z² groups.

11. The compound of any one of claims 1-9 wherein A is selected from:



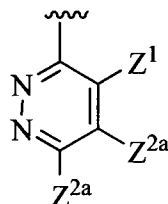
wherein each Z^{2a} is independently selected from H and Z^2 .

12. The compound of any one of claims 1-9 wherein A is:



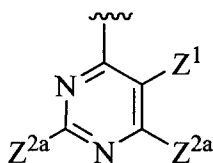
wherein each Z^{2a} is independently selected from H and Z^2 .

13. The compound of any one of claims 1-9 wherein A is:



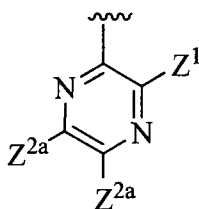
wherein each Z^{2a} is independently selected from H and Z^2 .

14. The compound of any one of claims 1-9 wherein A is:



wherein each Z^{2a} is independently selected from H and Z^2 .

15. The compound of any one of claims 1-9 wherein A is:



wherein each Z^{2a} is independently selected from H and Z^2 .

16. The compound of any one of claims 11-15 wherein each Z^{2a} is H.

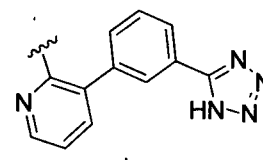
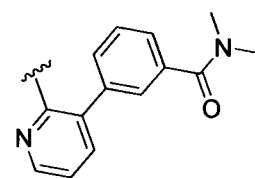
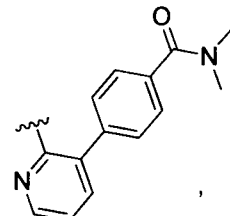
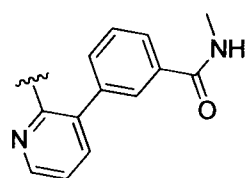
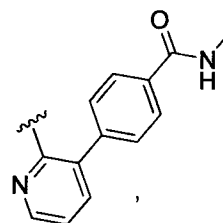
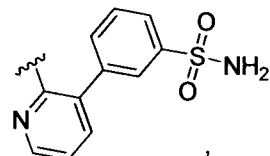
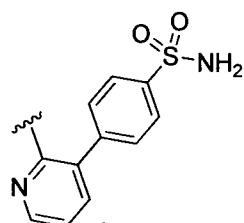
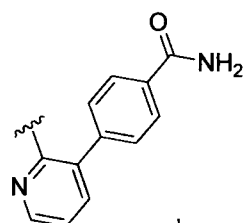
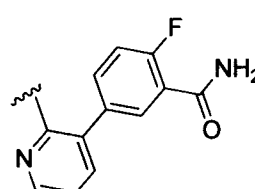
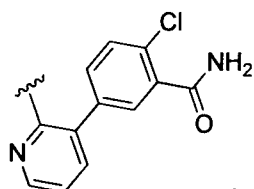
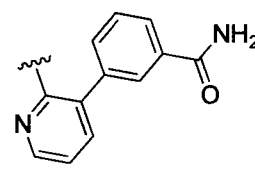
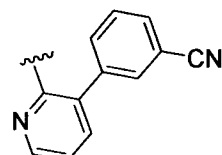
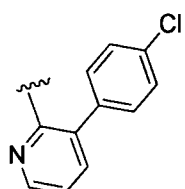
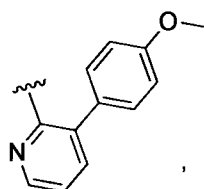
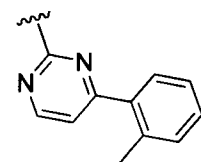
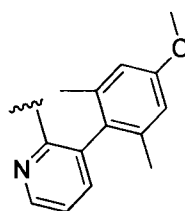
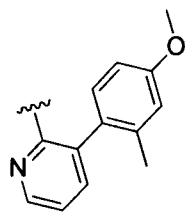
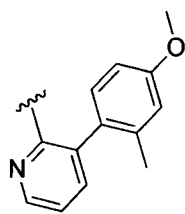
17. The compound of any one of claims 1-16 wherein each Z^1 is independently selected from (C_2-C_8) alkynyl, (C_3-C_7) carbocycle, aryl, heteroaryl and heterocycle, wherein any (C_3-C_7) carbocycle, aryl, heteroaryl, or heterocycle of Z^1 is optionally substituted with one or more Z^{1a} or Z^{1b} groups and wherein any (C_2-C_8) alkynyl of Z^1 is optionally substituted with one or more Z^{1a} groups.

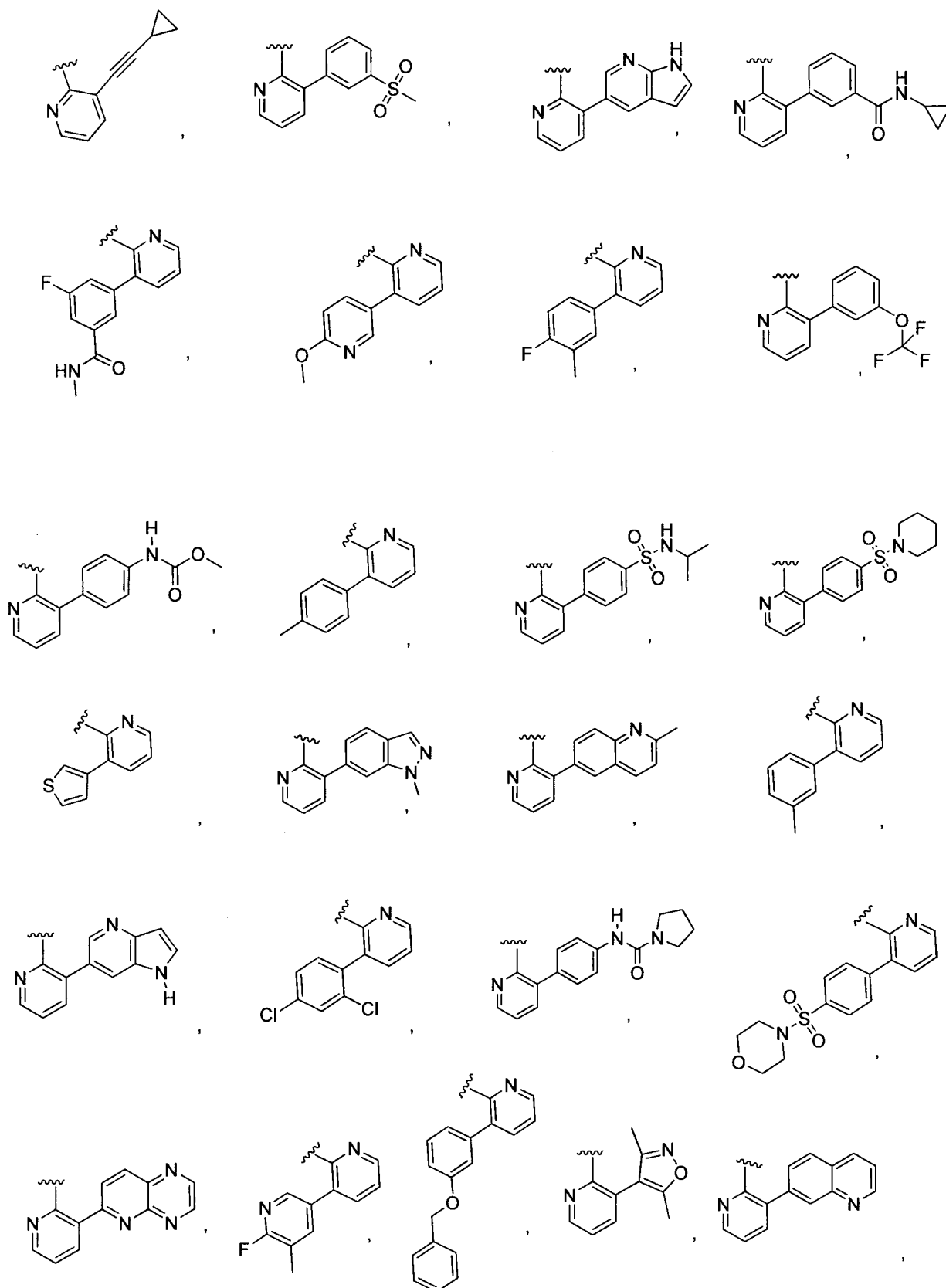
18. The compound of any one of claims 1-16 wherein Z^1 is selected from (C_2-C_8) alkynyl, aryl, heteroaryl and heterocycle, wherein any aryl, heteroaryl, or heterocycle of Z^1 is optionally substituted with one or more Z^{1a} or Z^{1b} groups and wherein any (C_2-C_8) alkynyl of Z^1 is optionally substituted with one or more Z^{1a} groups.

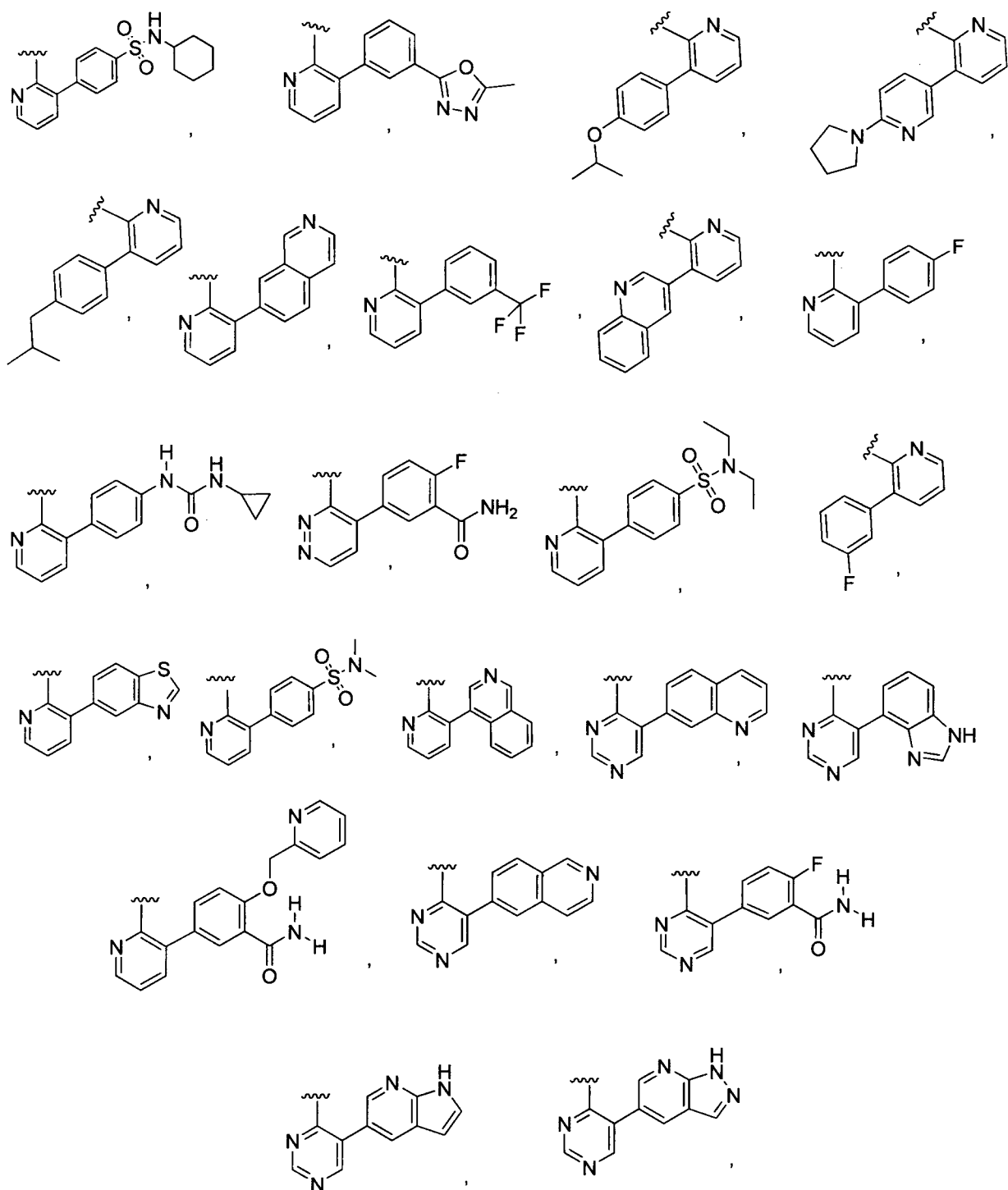
19. The compound of any one of claims 1-16 wherein Z^1 is selected from aryl, heteroaryl and heterocycle, wherein any aryl, heteroaryl, or heterocycle of Z^1 is optionally substituted with one or more Z^{1a} or Z^{1b} groups.

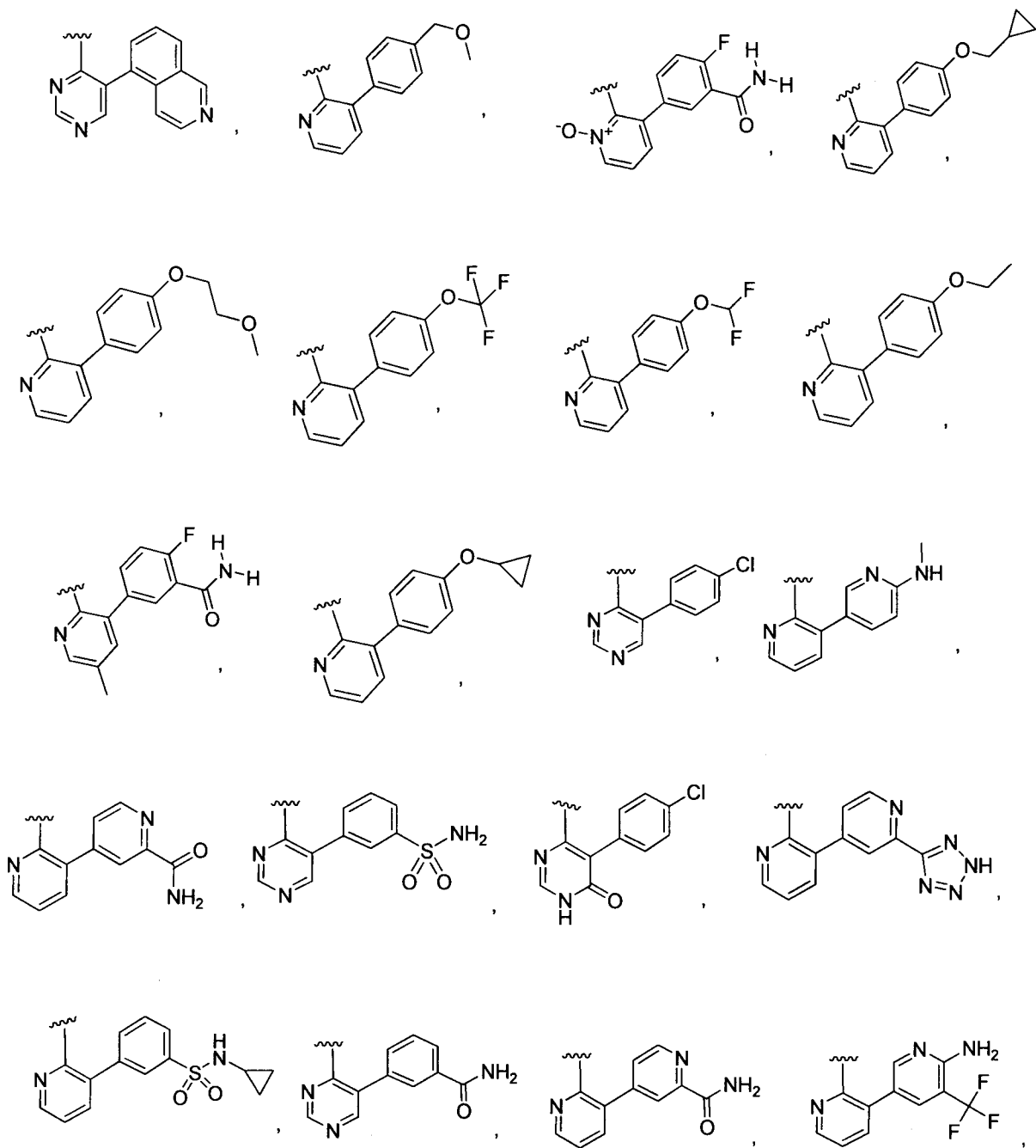
20. The compound of any one of claims 1-16 wherein each Z^{1a} is independently selected from aryl, heteroaryl, heterocycle, (C_3-C_7) carbocycle, halogen, -CN, $-OR_{n2}$, $-S(O)_2R_{p2}$, $-S(O)_2NR_{q2}R_{r2}$, $-NR_{q2}R_{r2}$, $-NR_{n2}COR_{p2}$, $-NR_{n2}CO_2R_{p2}$, $-NR_{n2}CONR_{q2}R_{r2}$, $-NR_{n2}S(O)_2R_{p2}$, $-C(O)R_{n2}$ and $-C(O)NR_{q2}R_{r2}$, wherein any aryl, heteroaryl, heterocycle and (C_3-C_7) carbocycle of Z^{1a} is optionally substituted with one or more Z^{1c} or Z^{1d} groups; and each Z^{1b} is independently selected from (C_1-C_8) alkyl and (C_2-C_8) alkynyl, wherein any (C_1-C_8) alkyl and (C_2-C_8) alkynyl of Z^{1b} is optionally substituted with one or more Z^{1c} groups.

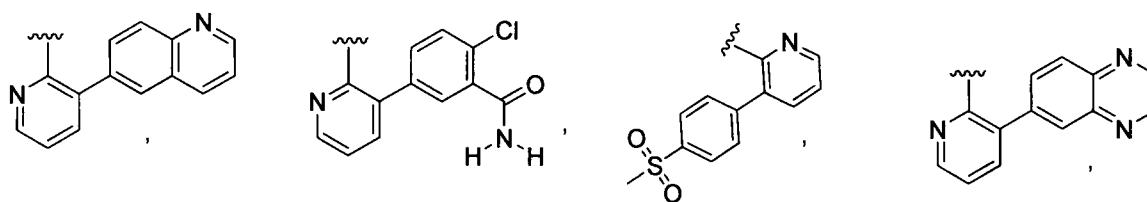
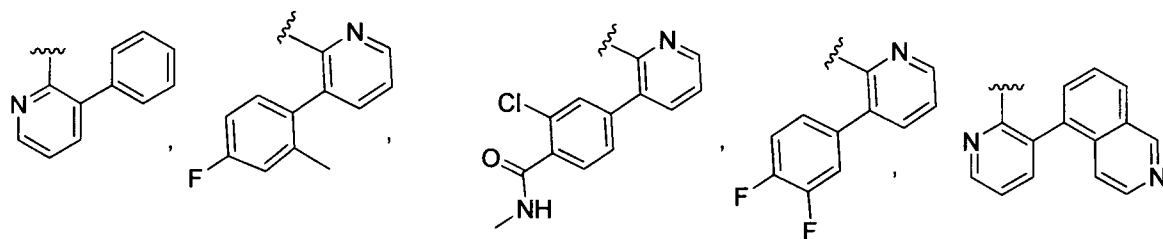
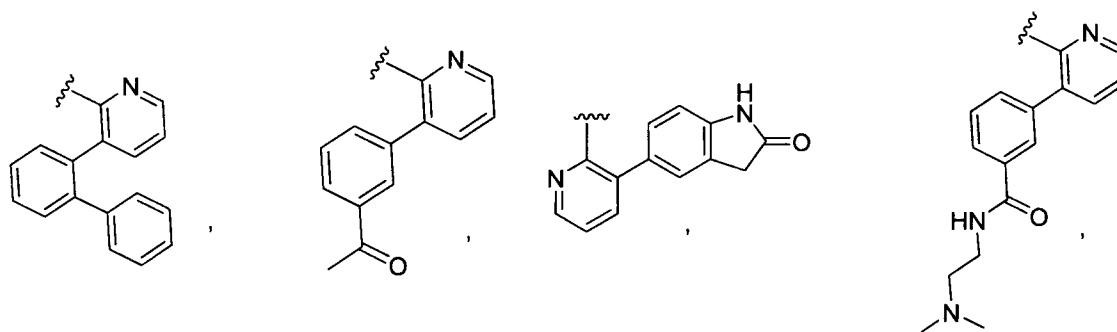
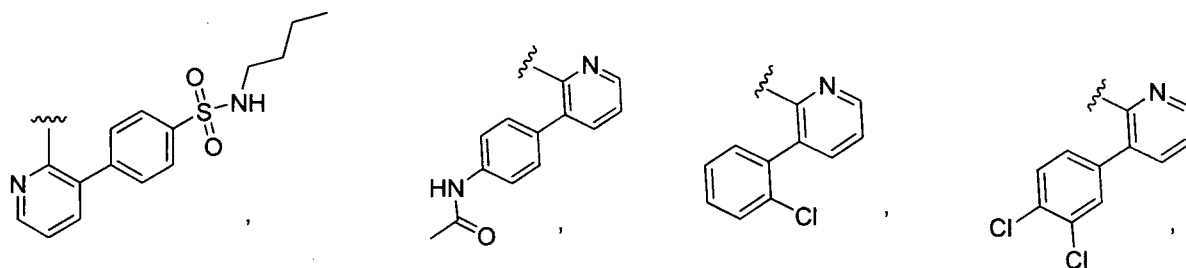
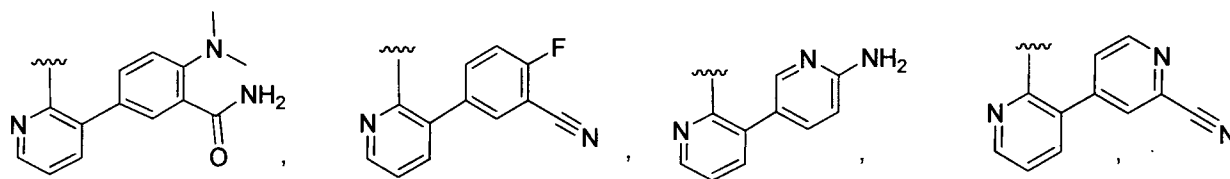
21. The compound of any one of claims 1-9 wherein A is selected from:

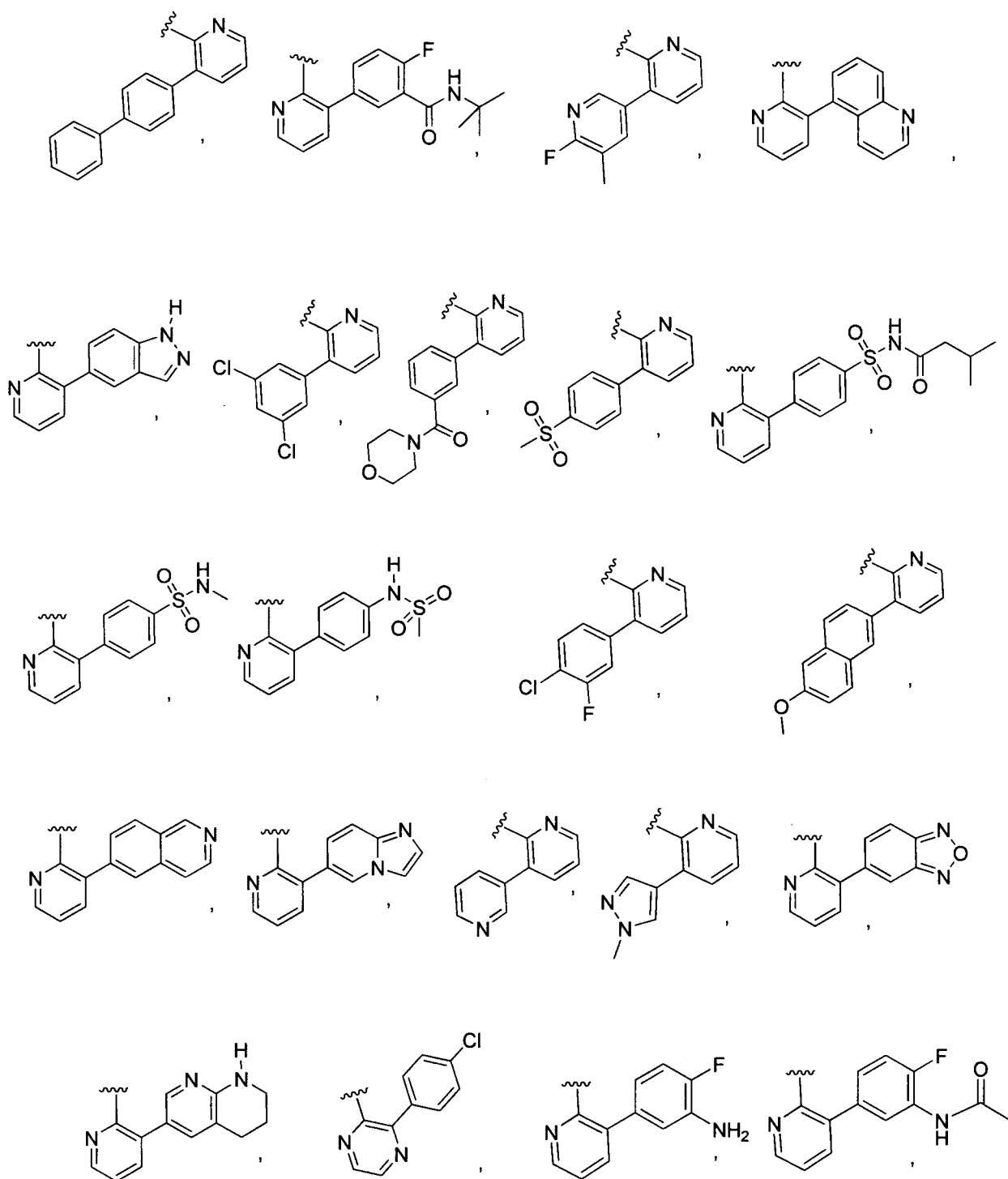


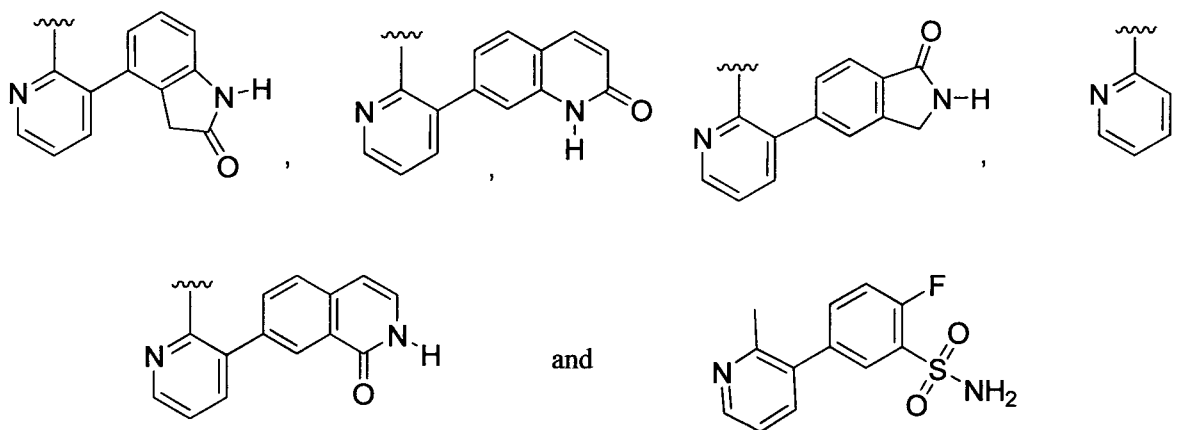




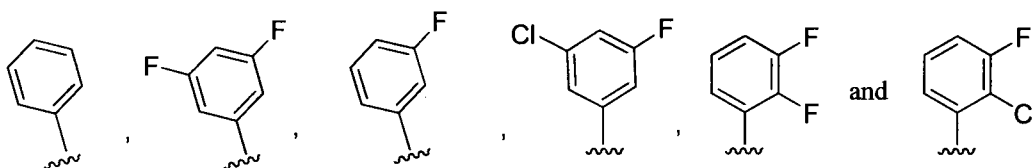








22. The compound of any one of claims 1-21 wherein R² is a 6-membered aryl wherein the 6-membered aryl is optionally substituted with one or more Z⁴ groups.
23. The compound of any one of claims 1-22 wherein each Z⁴ is independently selected from (C₁-C₈)alkyl, (C₃-C₇)carbocycle, halogen, and OR_{n6} wherein any (C₁-C₈)alkyl of Z⁴ is optionally substituted with one or more halogens.
24. The compound of any one claims 1-22 wherein each Z⁴ is independently selected from (C₃-C₇)carbocycle, halogen, methyl and -CN.
25. The compound of any one of claims 1-22 wherein each Z⁴ is halogen.
26. The compound of any one of claims 1-21 wherein R² is selected from:



27. The compound of any one of claims 1-26 wherein R¹ is heteroaryl or heterocycle, wherein any heteroaryl or heterocycle of R¹ is optionally substituted with one or more Z³ groups.
28. The compound of any one of claims 1-26 wherein R¹ is bicyclic-heteroaryl, tricyclic-heteroaryl, bicyclic-heterocycle or tricyclic-heterocycle, wherein any

bicyclic-heteroaryl, tricyclic-heteroaryl, bicyclic-heterocycle or tricyclic-heterocycle of R^1 is optionally substituted with one or more Z^3 groups.

29. The compound of any one of claims 1-26 wherein R^1 is tricyclic-heteroaryl or tricyclic-heterocycle, wherein any tricyclic-heteroaryl or tricyclic-heterocycle of R^1 is optionally substituted with one or more Z^3 groups.

30. The compound of any one of claims 1-26 wherein R^1 is bicyclic-heteroaryl, tricyclic-heteroaryl, bicyclic-heterocycle or tricyclic-heterocycle, wherein any bicyclic-heteroaryl, tricyclic-heteroaryl, bicyclic-heterocycle or tricyclic-heterocycle of R^1 contains at least one partially unsaturated ring, and wherein any bicyclic-heteroaryl, tricyclic-heteroaryl, bicyclic-heterocycle or tricyclic-heterocycle of R^1 is optionally substituted with one or more Z^3 groups.

31. The compound of any one of claims 1-26 wherein R^1 is tricyclic-heteroaryl or tricyclic-heterocycle, wherein any tricyclic-heteroaryl or tricyclic-heterocycle of R^1 contains one aromatic ring, one partially unsaturated ring, and one fully saturated ring, and wherein any tricyclic-heteroaryl or tricyclic-heterocycle of R^1 is optionally substituted with one or more Z^3 groups.

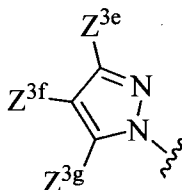
32. The compound of any one of claims 1-26 wherein R^1 is bicyclic-heteroaryl, tricyclic-heteroaryl, bicyclic-heterocycle or tricyclic-heterocycle, wherein any bicyclic-heteroaryl, tricyclic-heteroaryl, bicyclic-heterocycle or tricyclic-heterocycle of R^1 contains 5 or more halogen atoms, and wherein any bicyclic-heteroaryl, tricyclic-heteroaryl, bicyclic-heterocycle or tricyclic-heterocycle of R^1 is optionally additionally substituted with one or more Z^3 groups.

33. The compound of any one of claims 1-26 wherein R^1 is tricyclic-heteroaryl or tricyclic-heterocycle, wherein any tricyclic-heteroaryl or tricyclic-heterocycle of R^1 contains a bridged bicyclic carbocycle or a bridged bicyclic heterocycle, and wherein any tricyclic-heteroaryl or tricyclic-heterocycle of R^1 is optionally substituted with one or more Z^3 groups.

34. The compound of any one of claims 1-26 wherein R^1 is tricyclic-heteroaryl or tricyclic-heterocycle, wherein any tricyclic-heteroaryl or tricyclic-heterocycle of R^1 contains a

spiro-connected bicyclic carbocycle or a spiro-connected bicyclic heterocycle, and wherein any tricyclic-heteroaryl or tricyclic-heterocycle of R^1 is optionally substituted with one or more Z^3 groups.

35. The compound of any one of claims 1-26 wherein R^1 is:



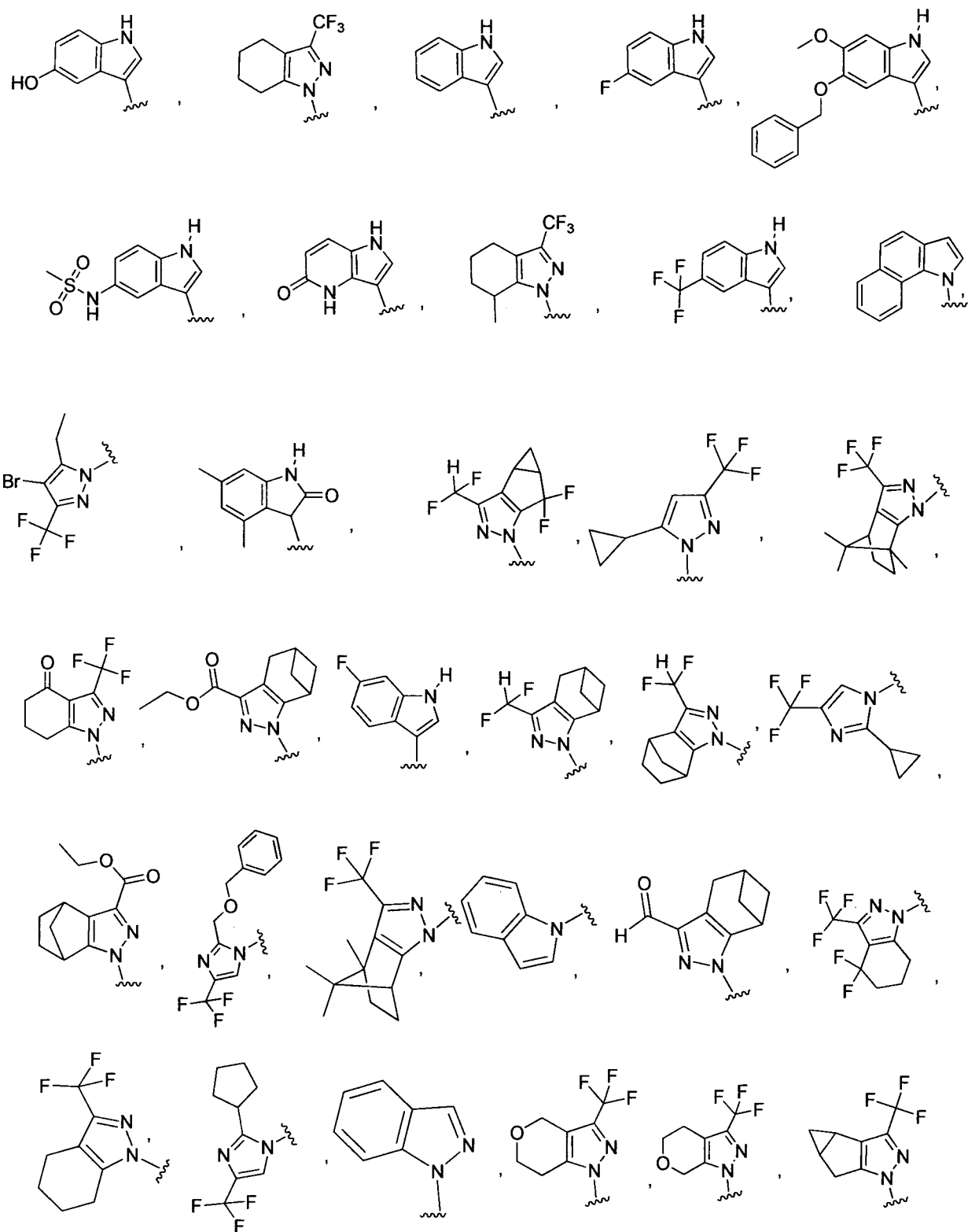
wherein Z^{3e} , Z^{3f} , and Z^{3g} are each independently selected from H and Z^3 ; or Z^{3e} is H or Z^3 , and Z^{3f} and Z^{3g} together with the carbons to which they are attached form a 5, 6, or 7-membered heterocycle or a 5, 6, or 7-membered carbocycle, which 5, 6, or 7-membered heterocycle or a 5, 6, or 7-membered carbocycle is optionally substituted with one or more Z^3 groups.

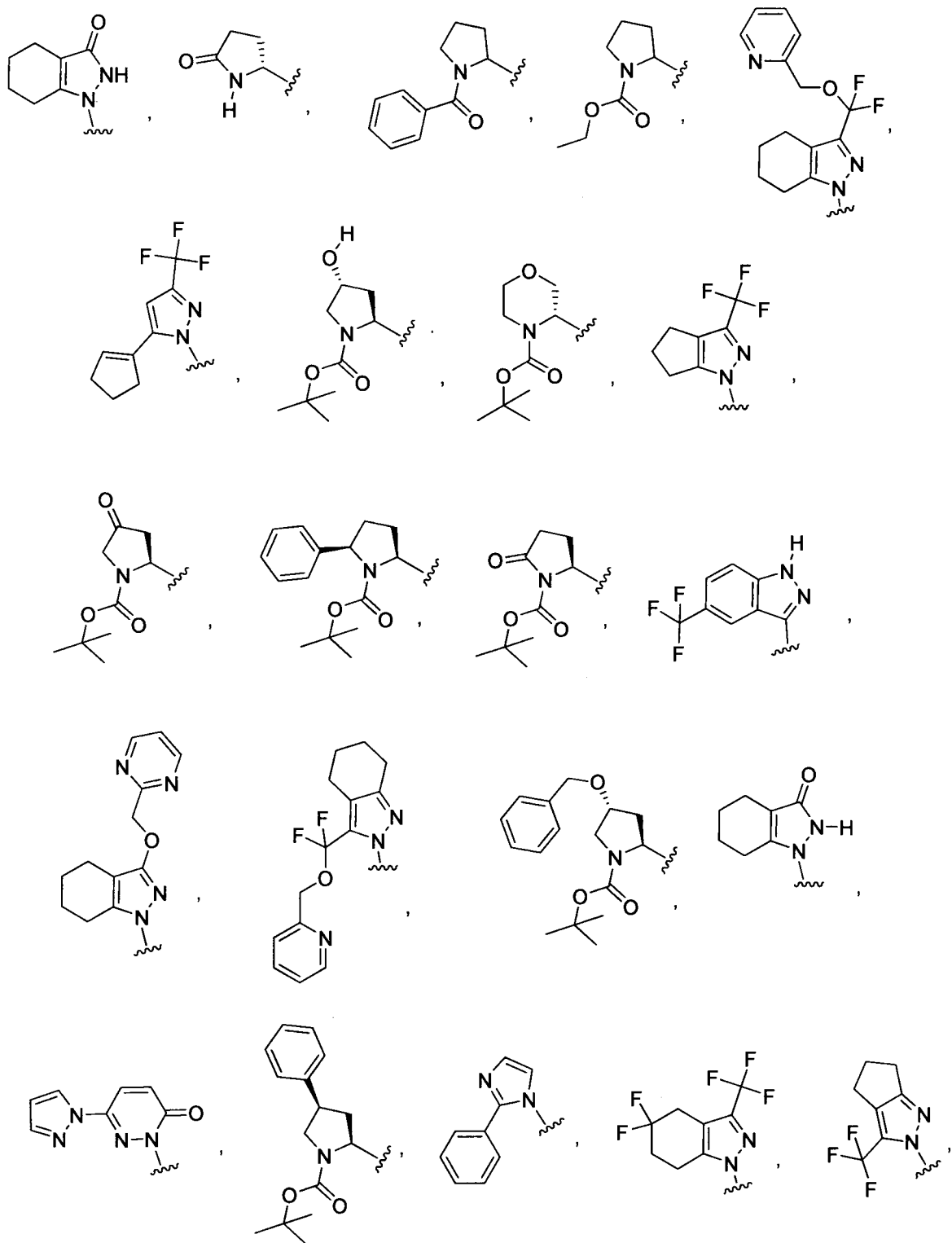
36. The compound of any one of claims 1-35 wherein each Z^3 is independently selected from (C_1-C_8) alkyl, (C_2-C_8) alkenyl, (C_2-C_8) alkynyl, (C_3-C_7) carbocycle, aryl, halogen, -CN, $-OR_{n4}$, $-S(O)_2R_{p4}$, $-NR_{n4}CO_2R_{p4}$, $-NR_{n4}S(O)_2R_{p4}$, $-C(O)R_{n4}$, $-C(O)OR_{n4}$, $-C(O)NR_{q4}R_{r4}$ and $-B(OR_{q4})(OR_{r4})$ wherein any (C_3-C_7) carbocycle and aryl of Z^3 is optionally substituted with one or more Z^{3a} or Z^{3b} groups, and wherein any (C_1-C_8) alkyl, (C_2-C_8) alkenyl and (C_2-C_8) alkynyl of Z^3 is optionally substituted with one or more Z^{3a} groups.

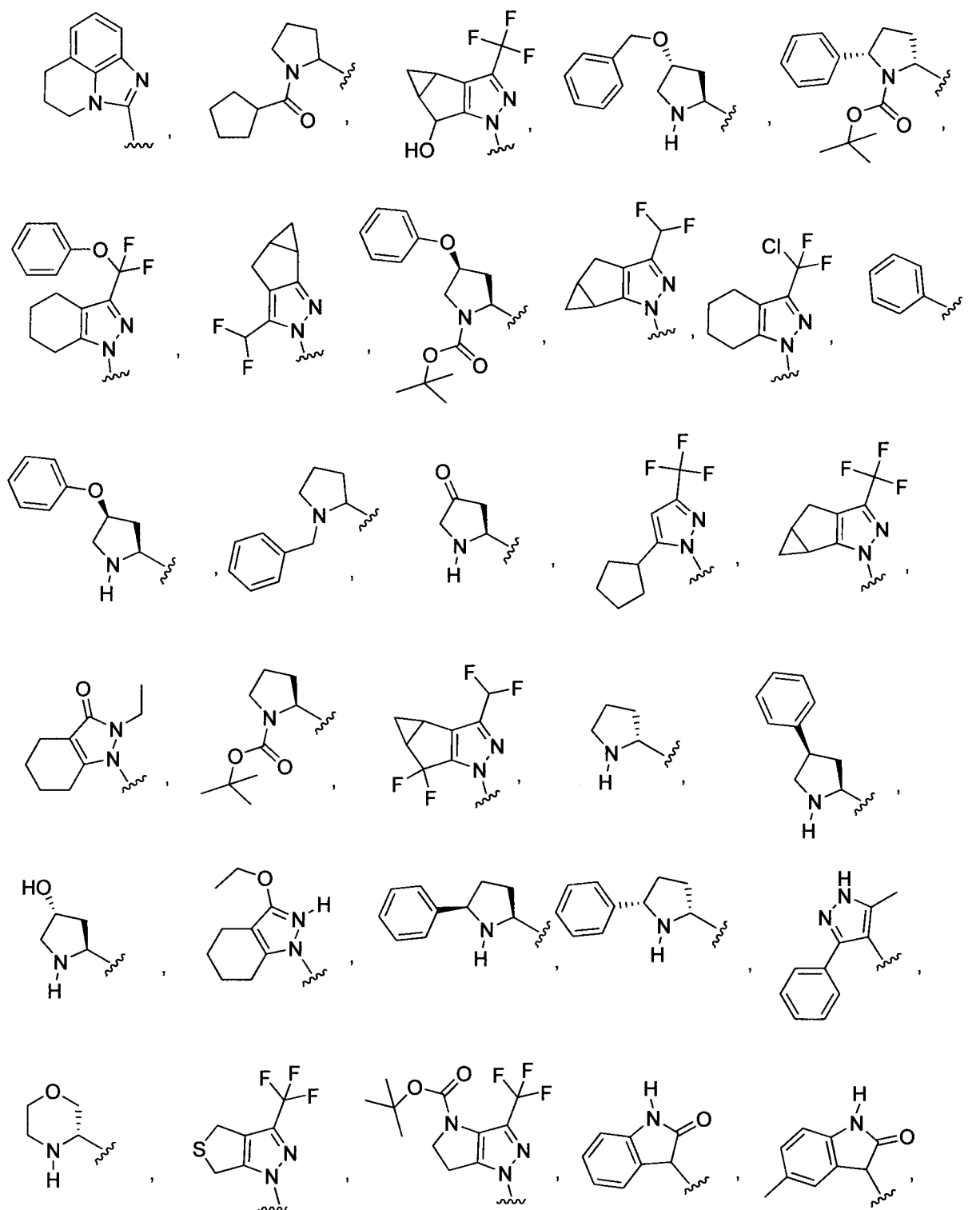
37. The compound of any one of claims 1-35 wherein each Z^3 is independently selected from (C_1-C_8) alkyl, (C_2-C_8) alkenyl, (C_2-C_8) alkynyl, (C_3-C_7) carbocycle, aryl, halogen, -CN, $-OR_{n4}$, $-S(O)_2R_{p4}$, $-NR_{n4}S(O)_2R_{p4}$, $-S(O)_2NR_{q4}R_{r4}$, $-NR_{q4}R_{r4}$, $-C(O)R_{n4}$, $-C(O)NR_{q4}R_{r4}$ and $-NR_{n4}COR_{q4}$ wherein any (C_3-C_7) carbocycle and aryl of Z^3 is optionally substituted with one or more Z^{3a} or Z^{3b} groups, and wherein any (C_1-C_8) alkyl, (C_2-C_8) alkenyl and (C_2-C_8) alkynyl of Z^3 is optionally substituted with one or more Z^{3a} groups.

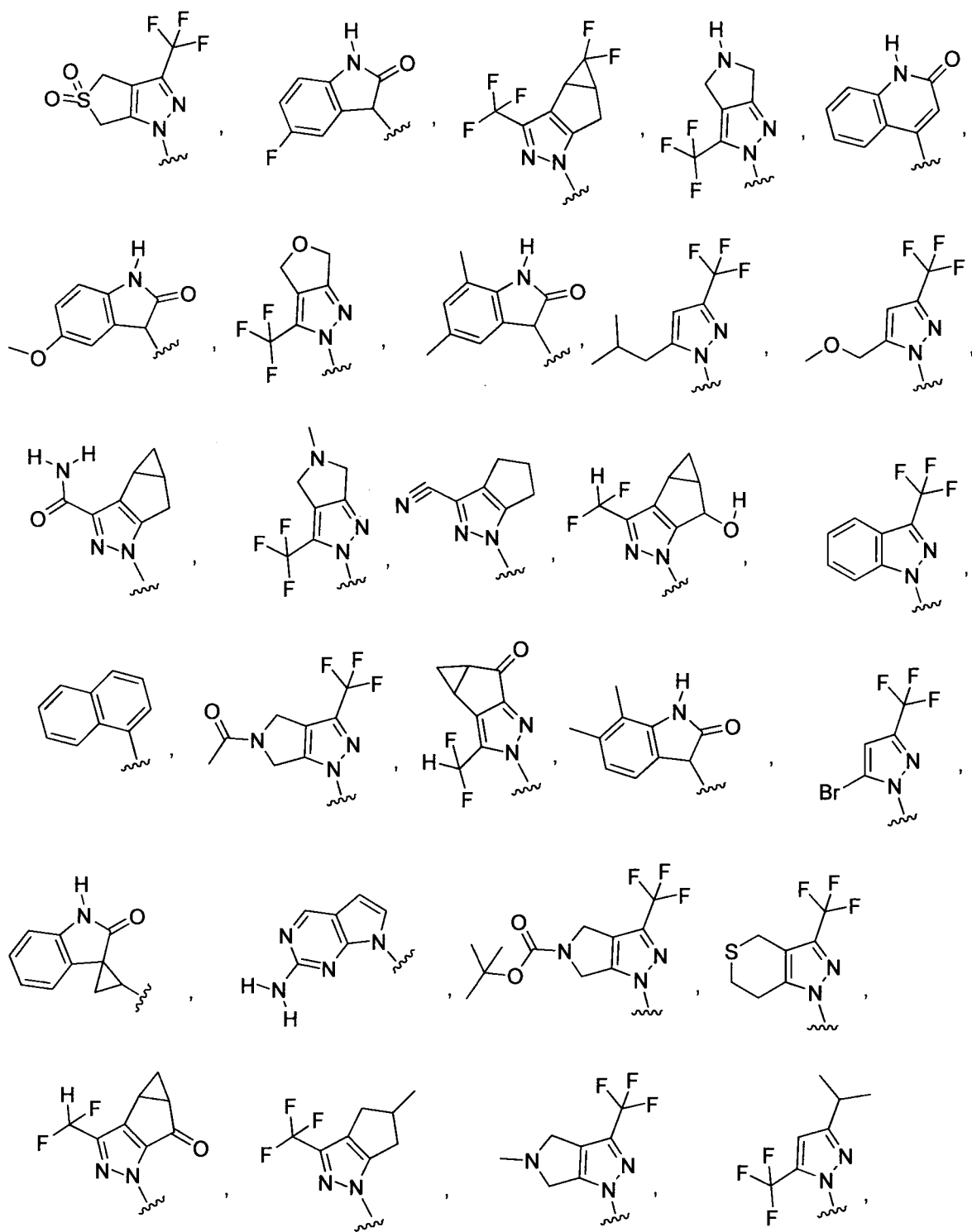
38. The compound of any one of claims 1-35 wherein each Z^3 is independently selected from methyl, trifluoromethyl, hydroxy, methoxy, benzyloxy, fluoro, $-NHSO_2CH_3$, 2-hydroxyprop-2-yl, difluoromethyl and amino.

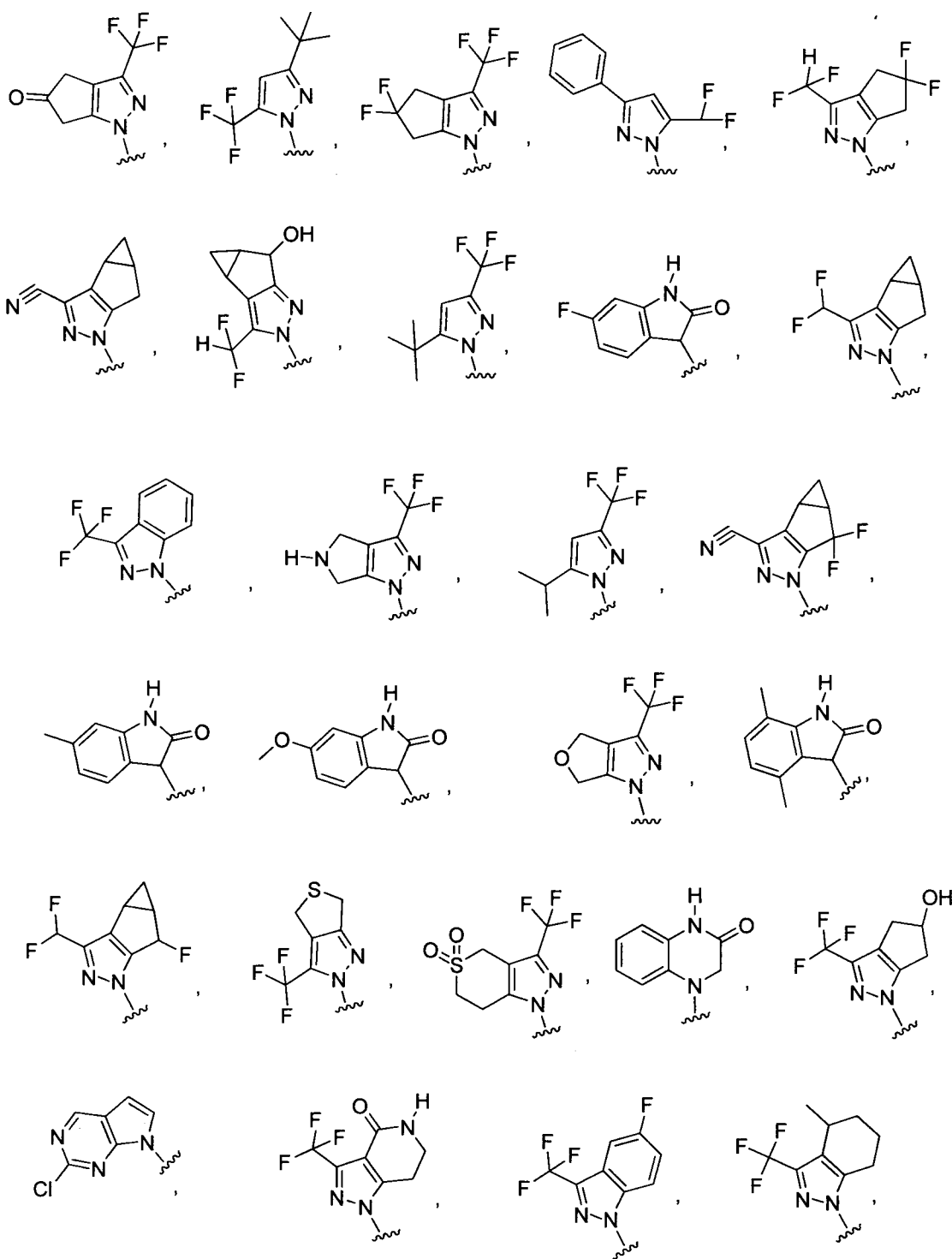
39. The compound of any one of claims 1-35 wherein R^1 is selected from:

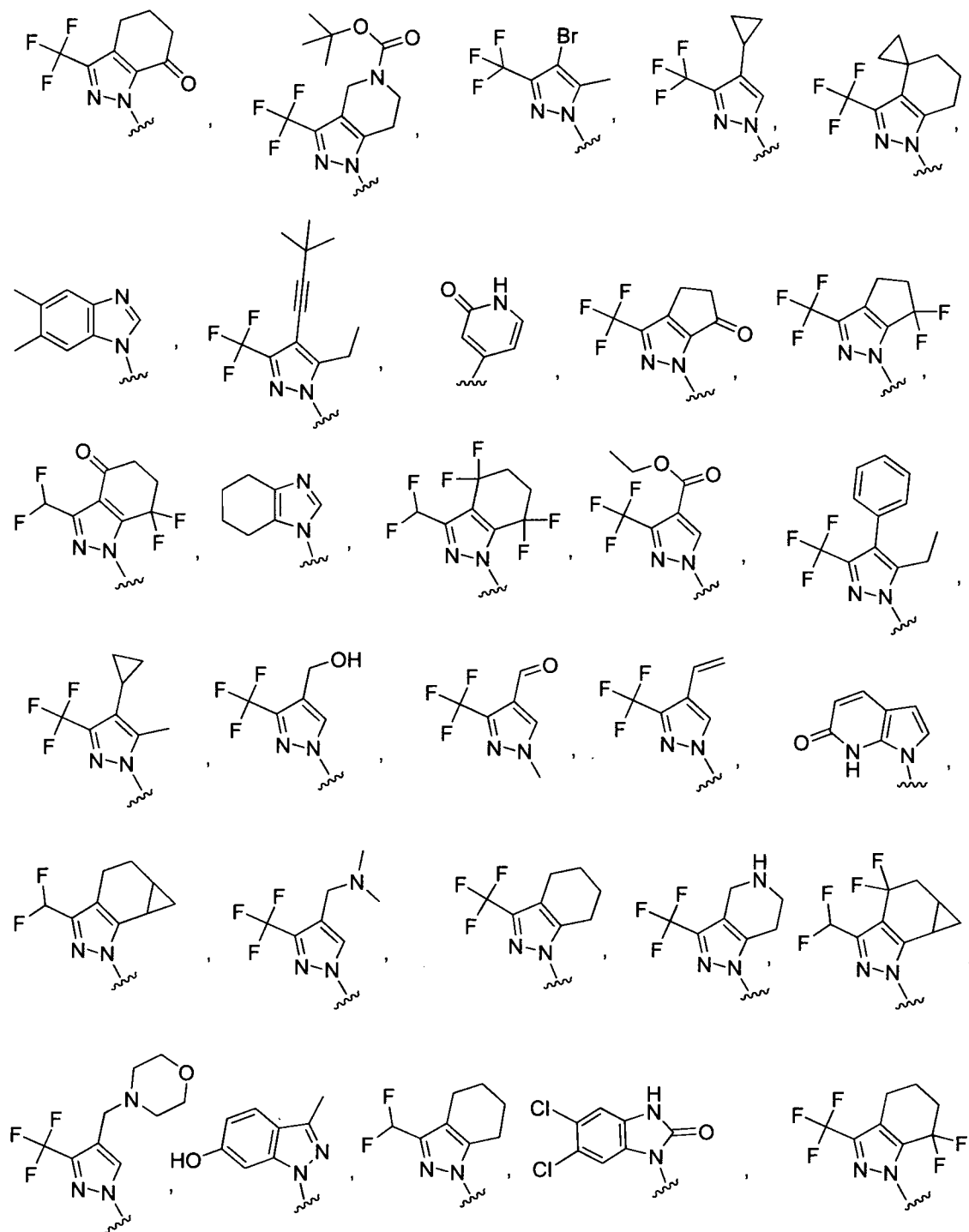


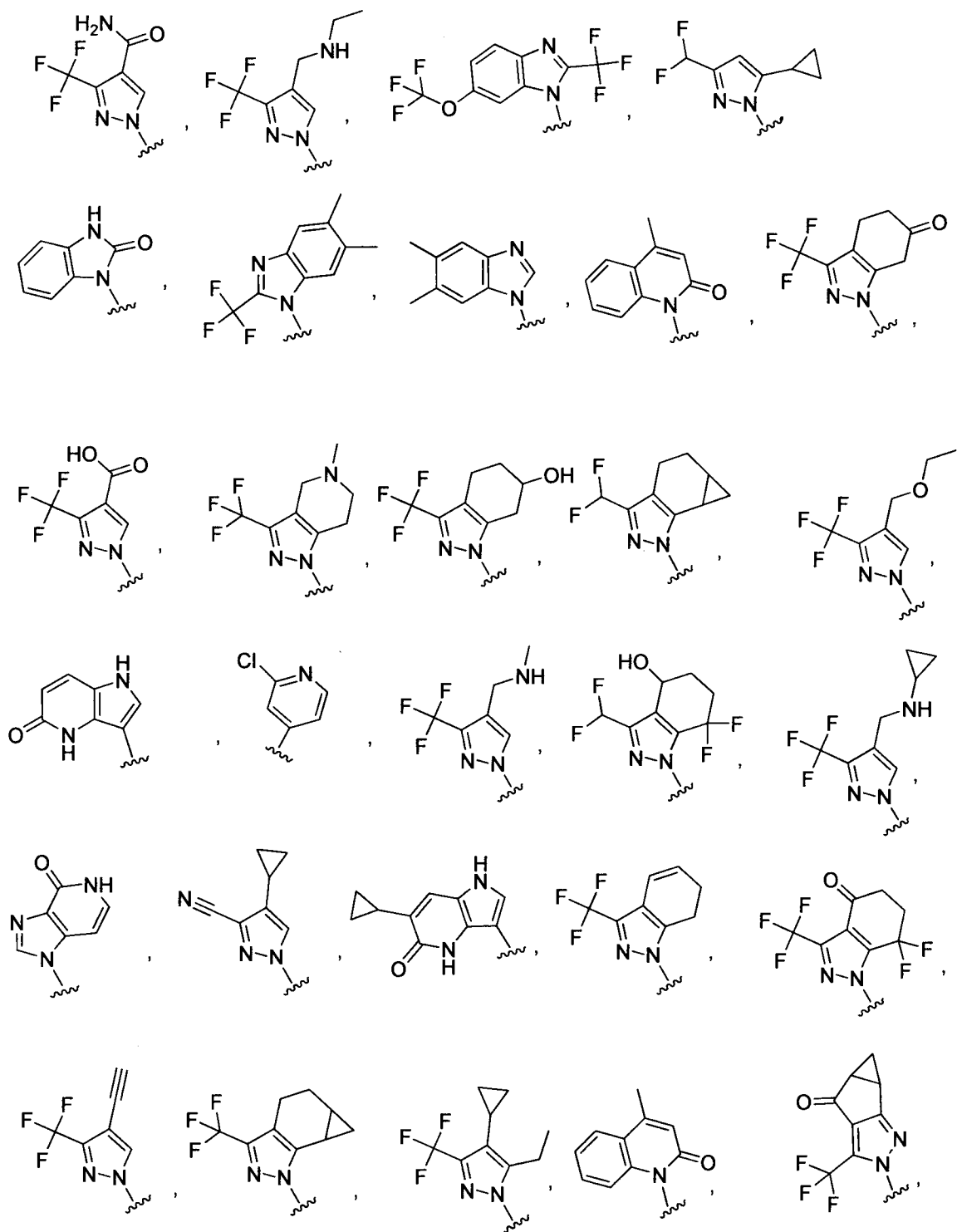


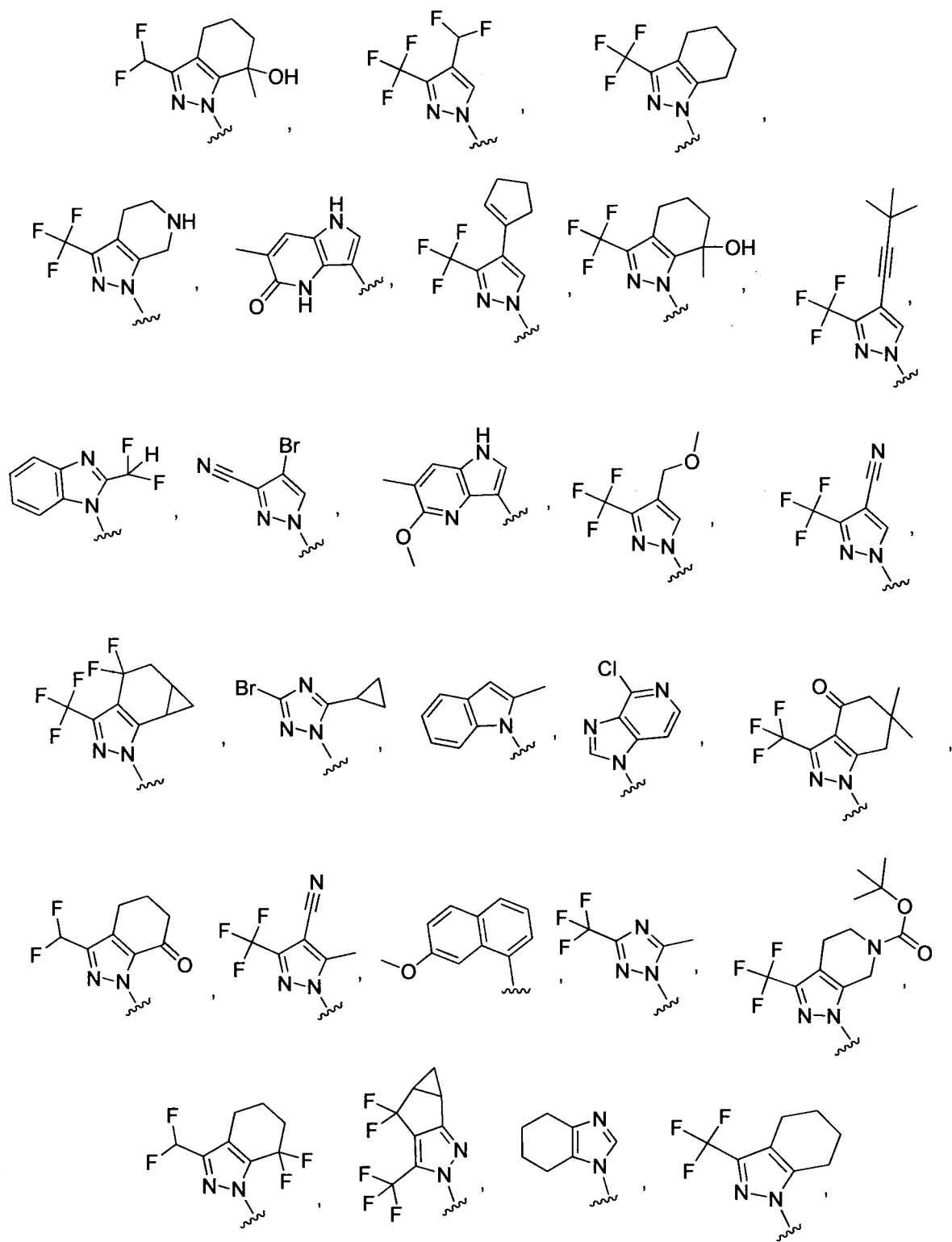


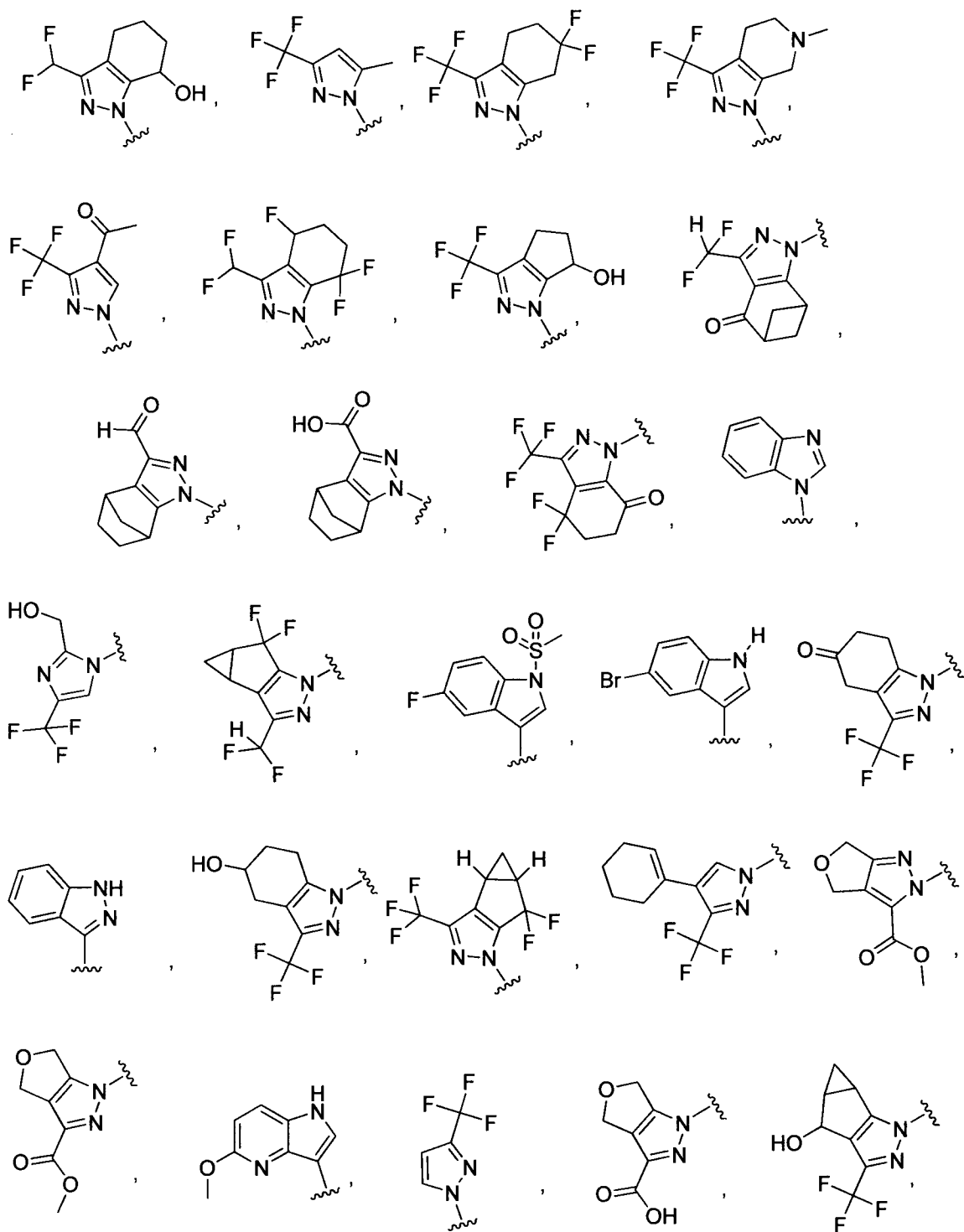


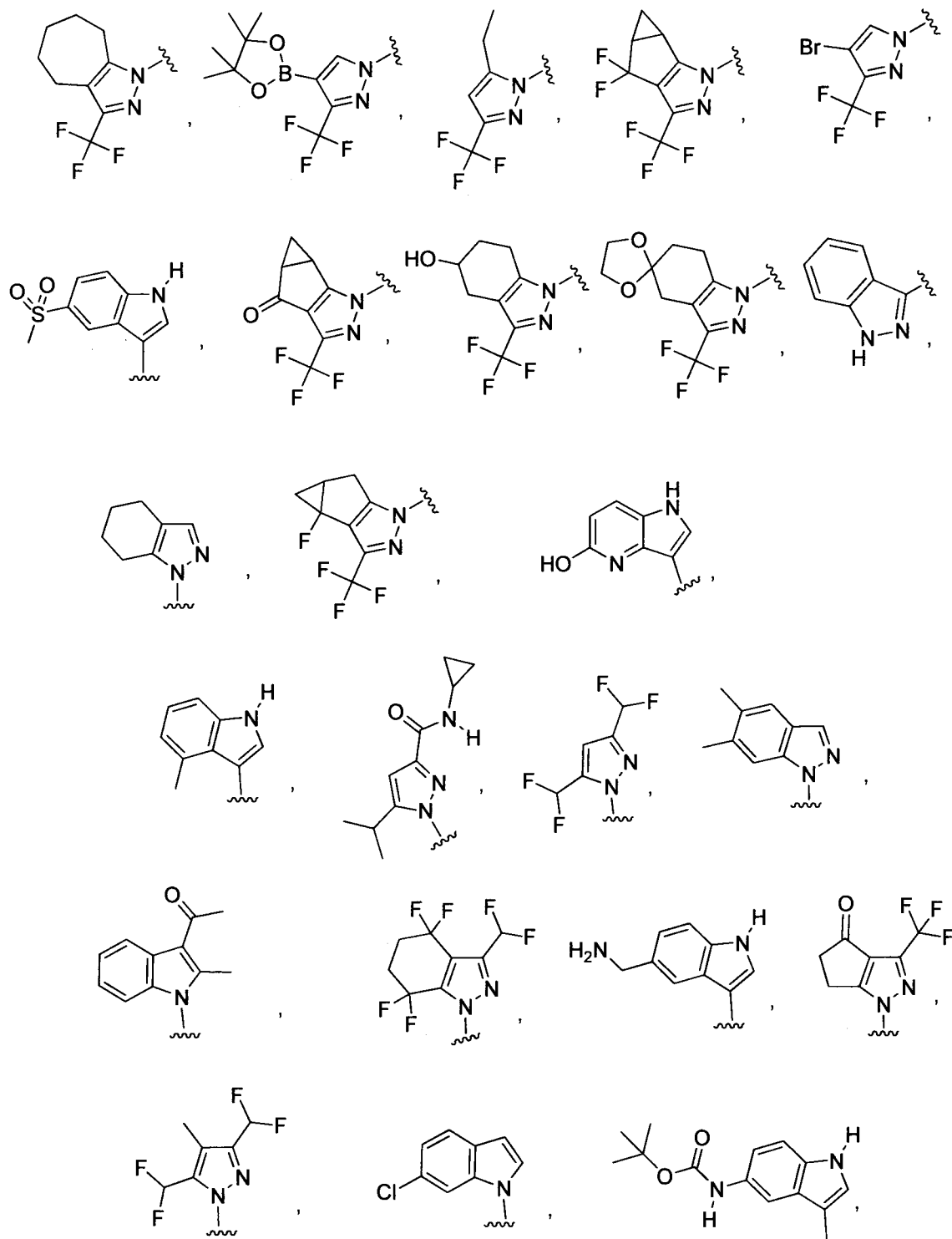


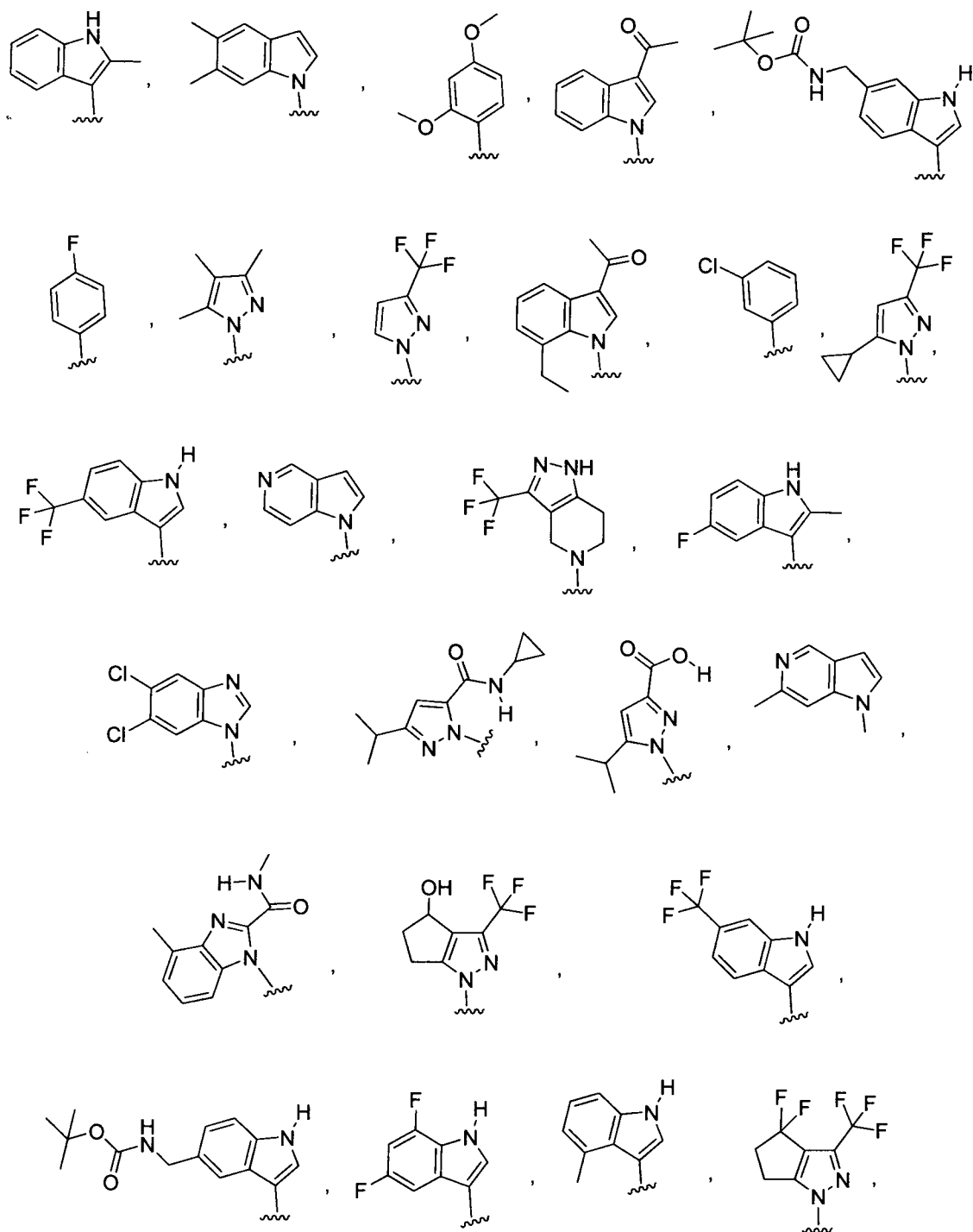


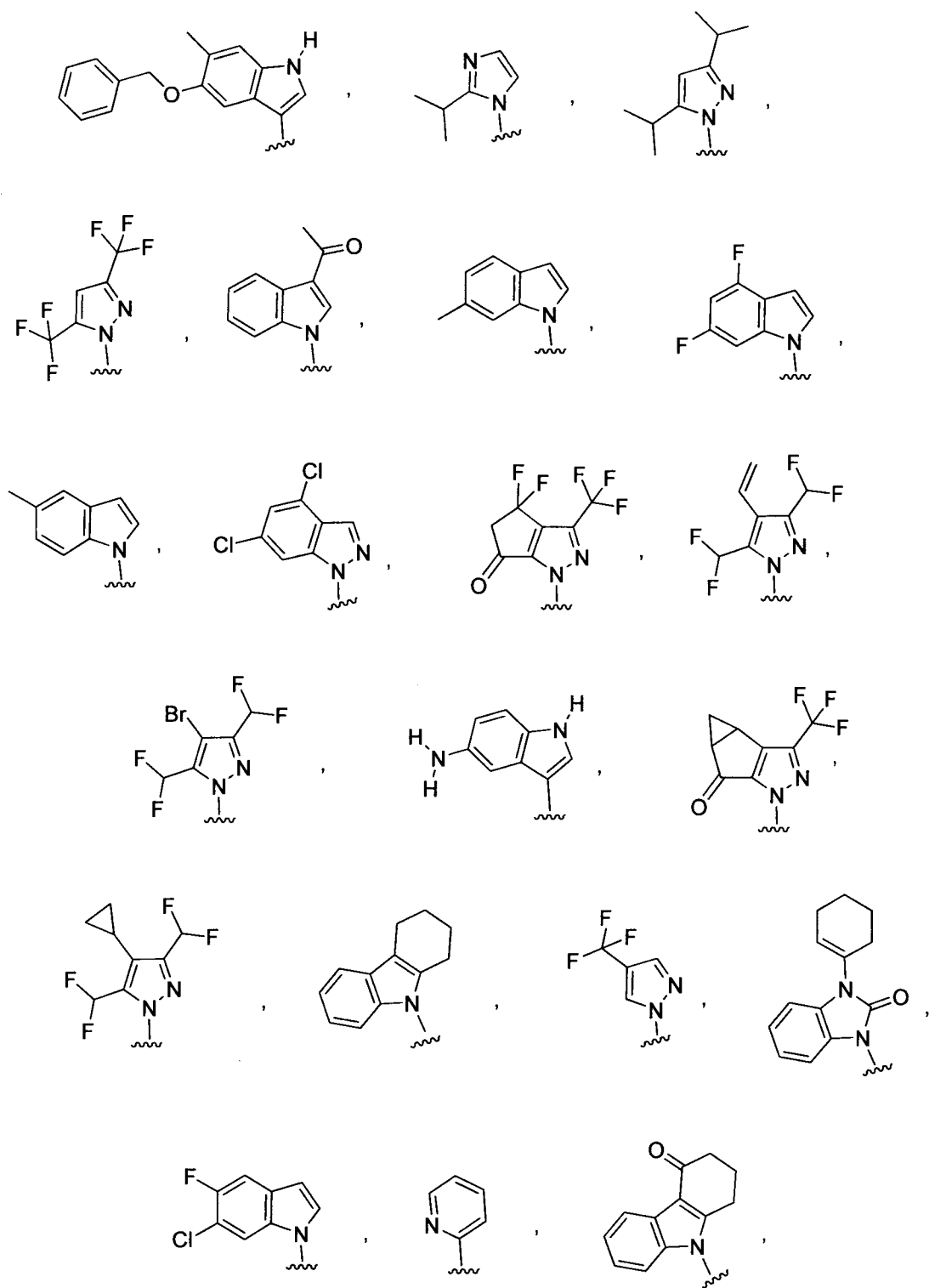




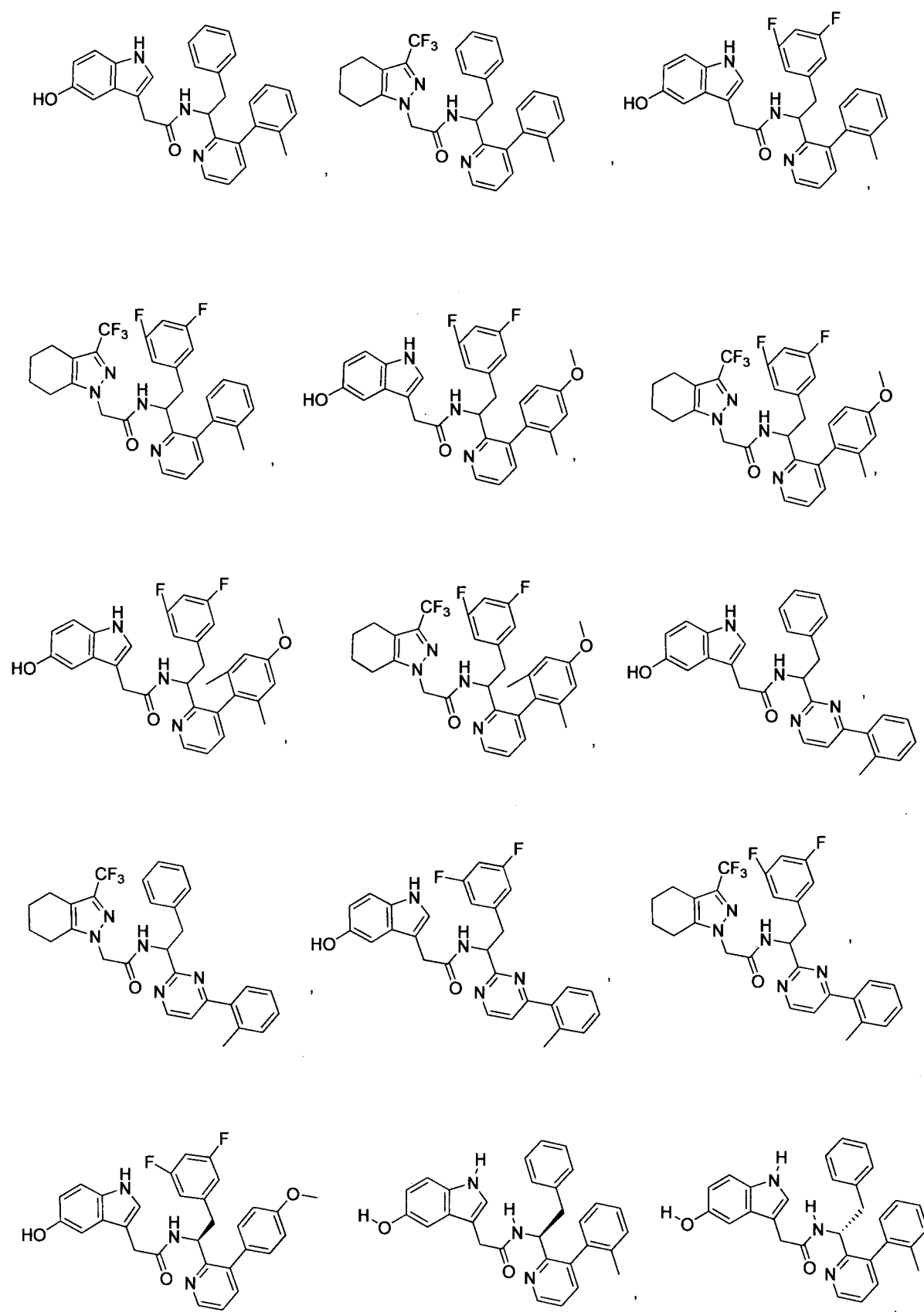


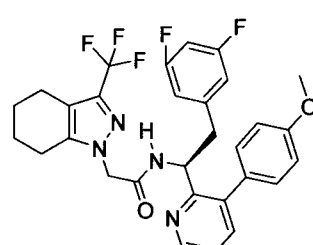
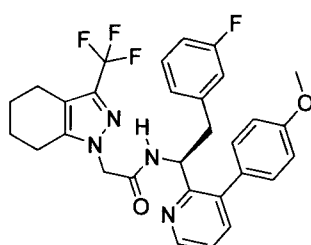
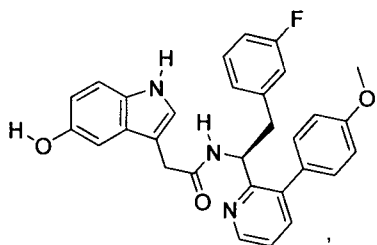
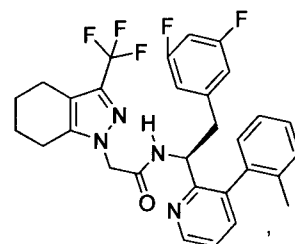
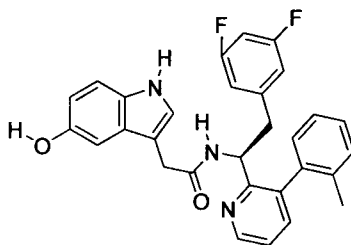
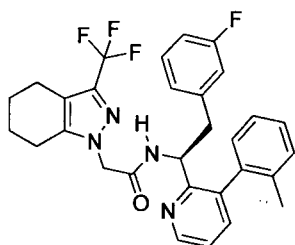
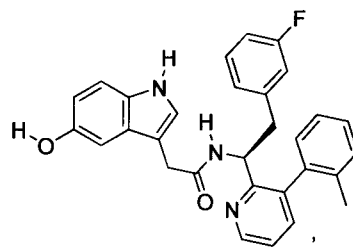
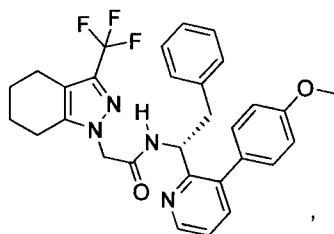
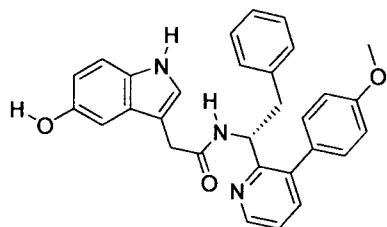
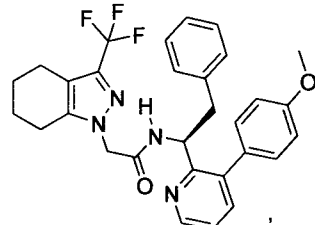
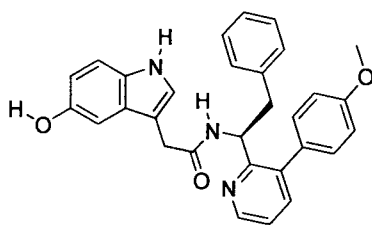
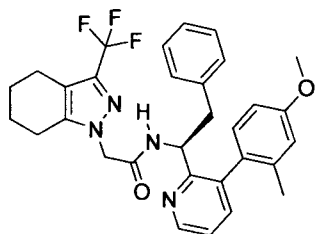
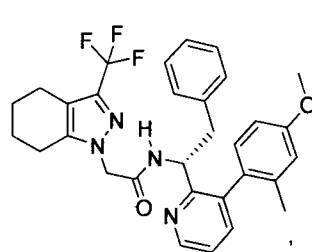
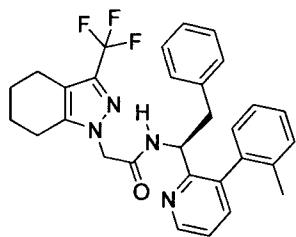
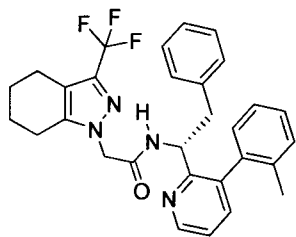


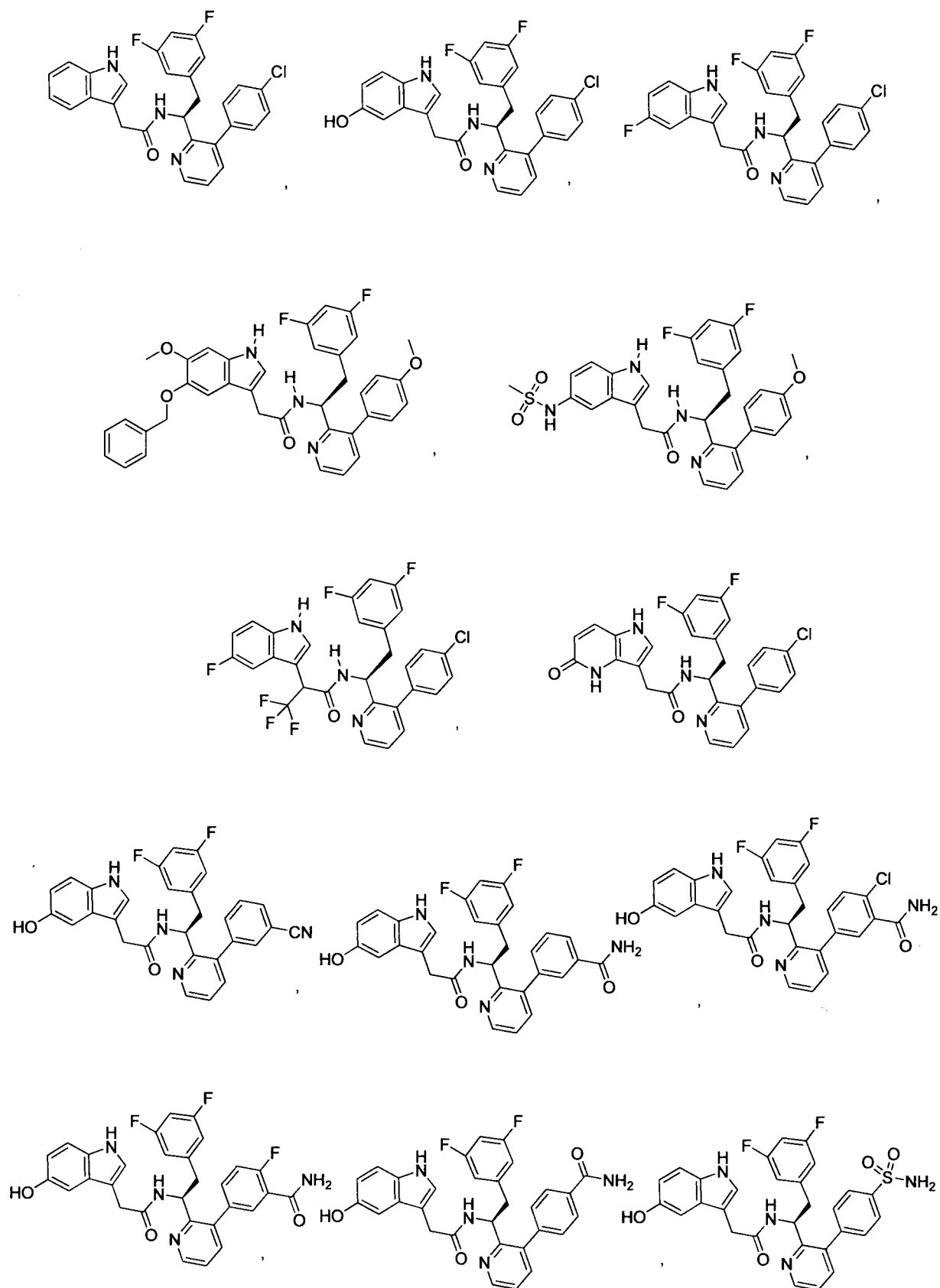


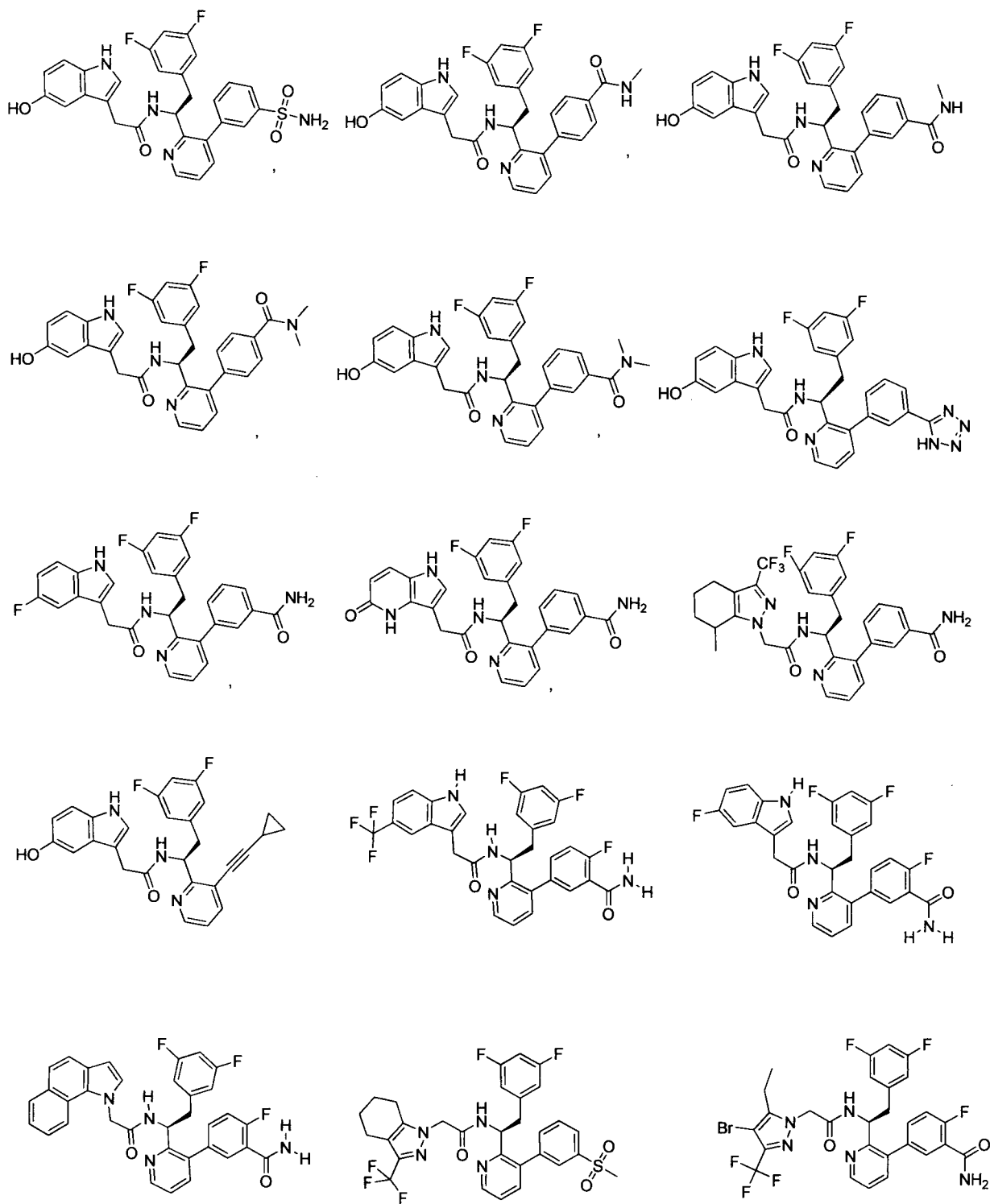


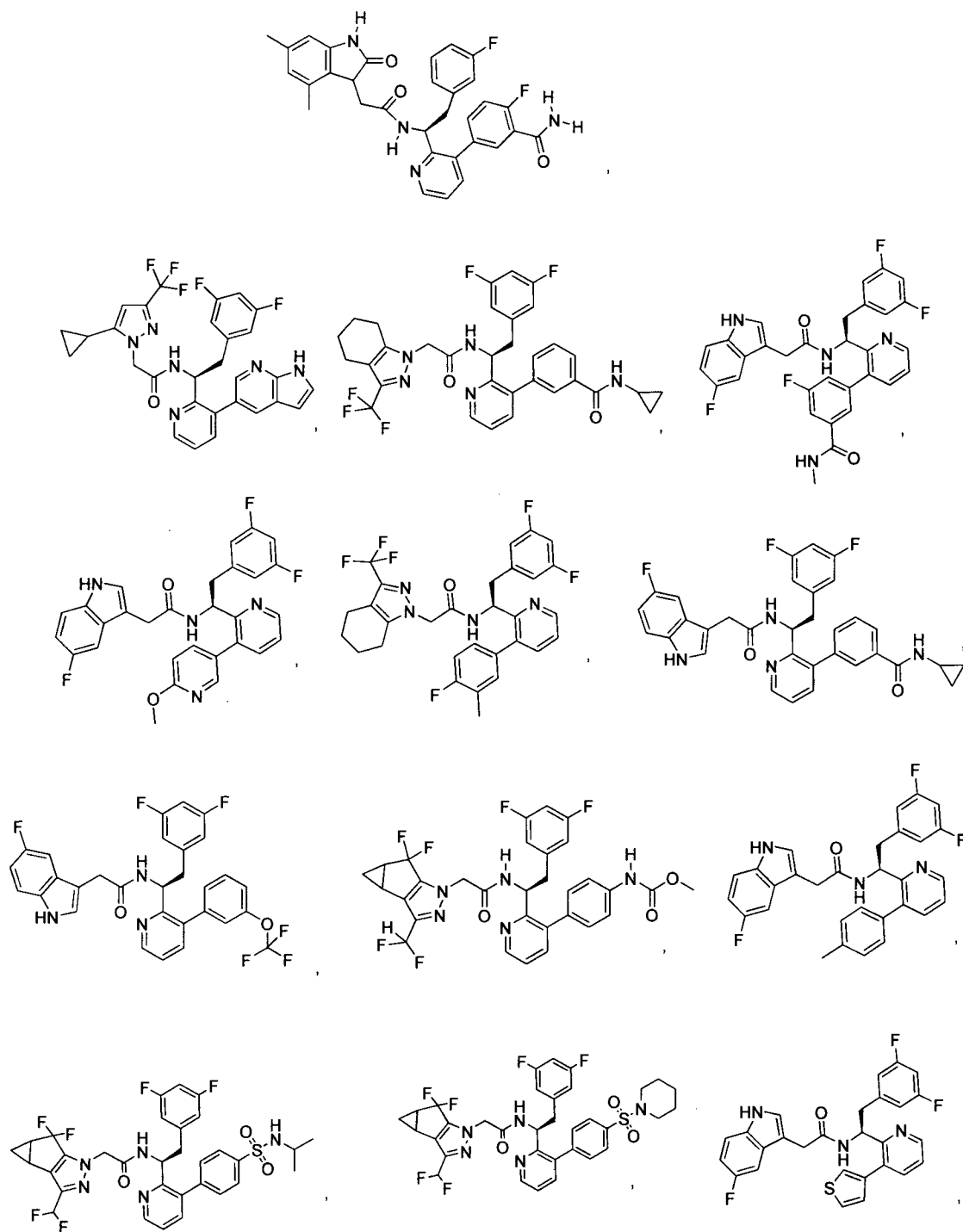
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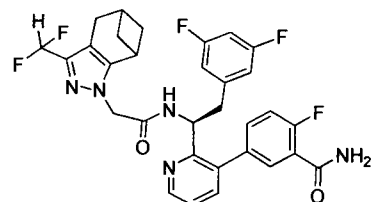
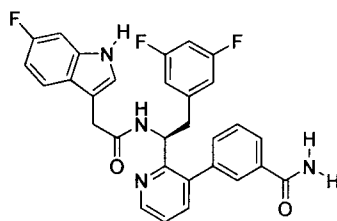
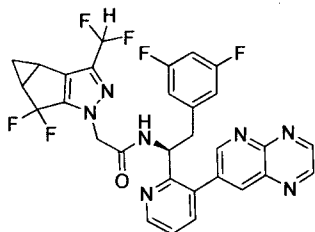
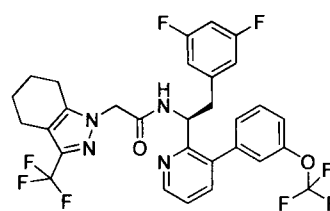
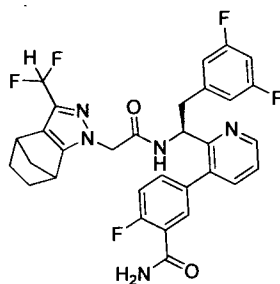
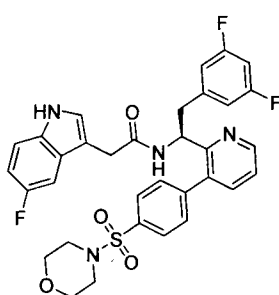
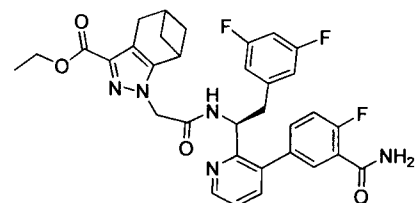
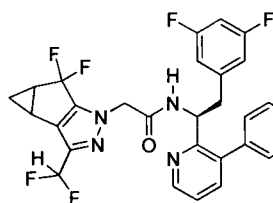
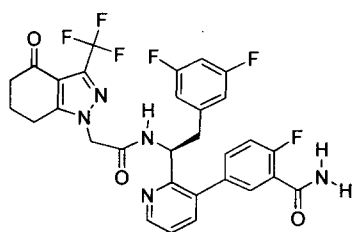
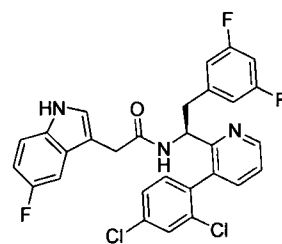
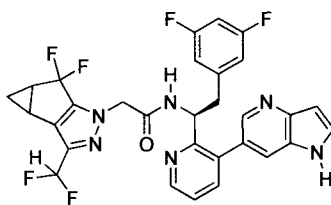
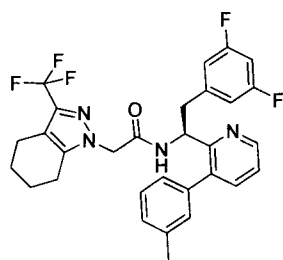
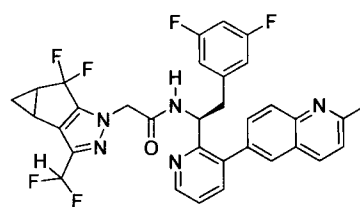
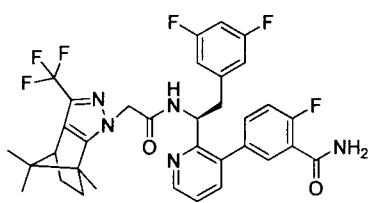
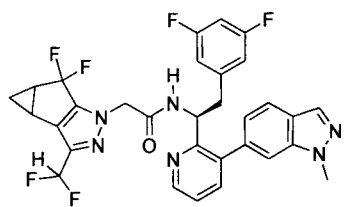


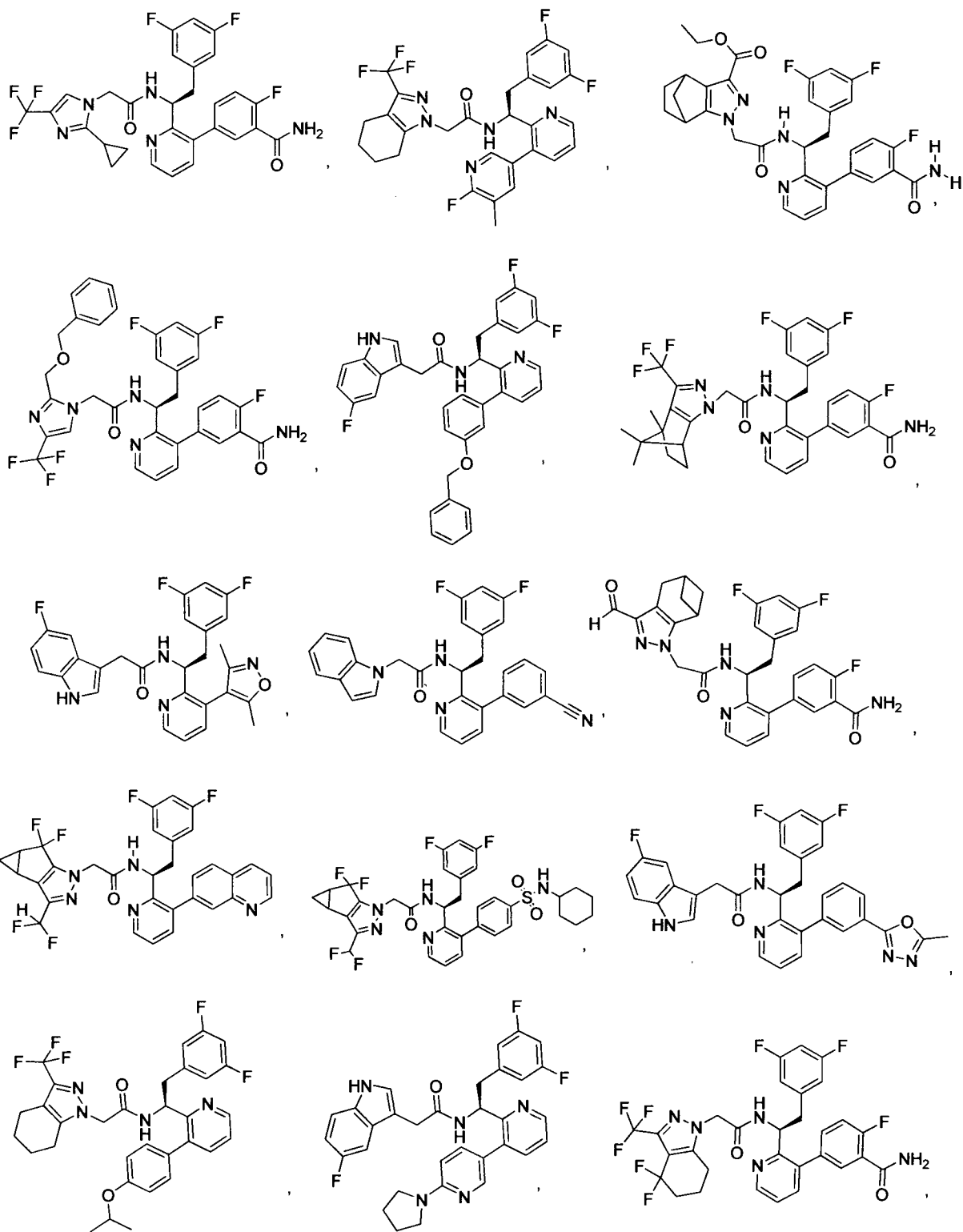


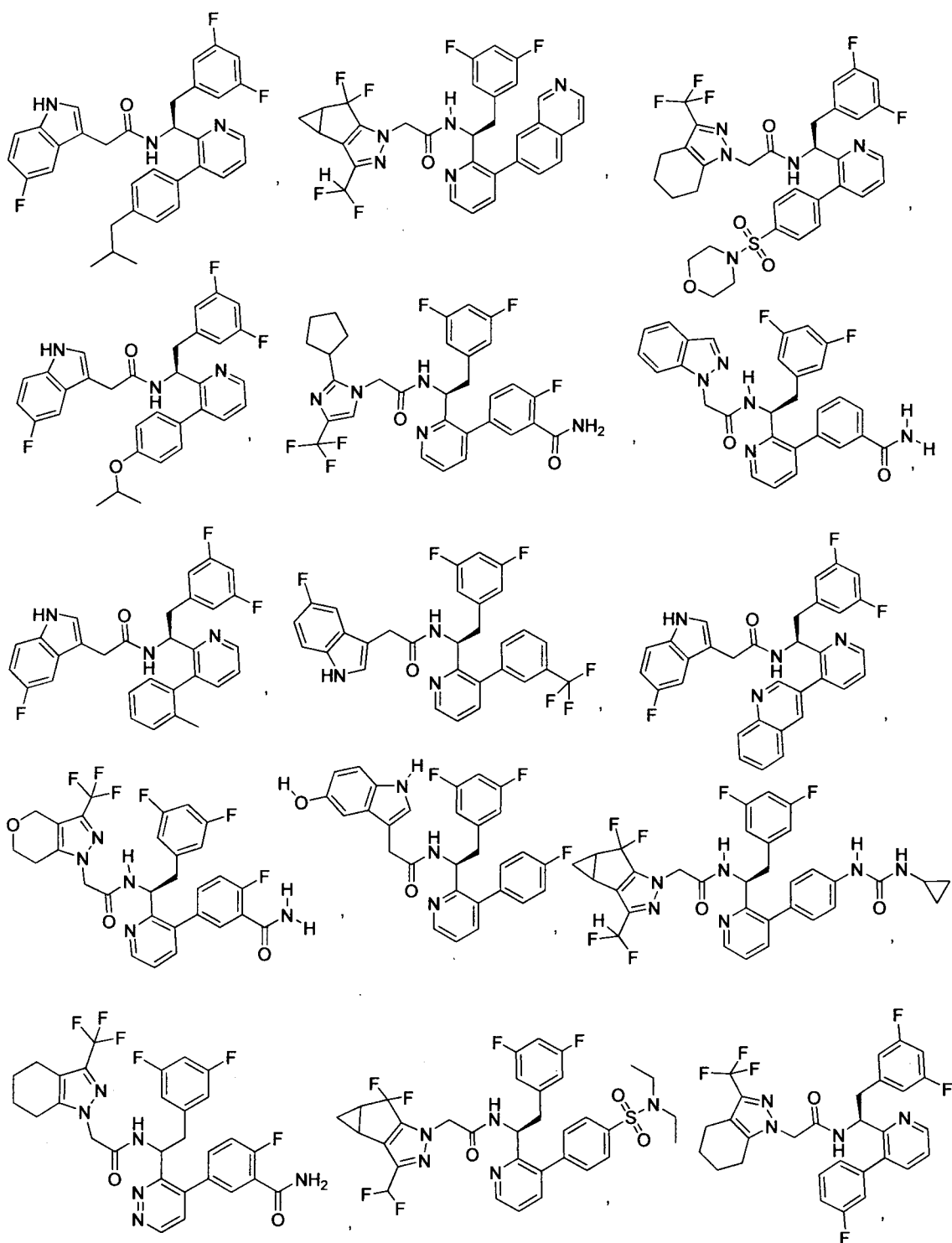


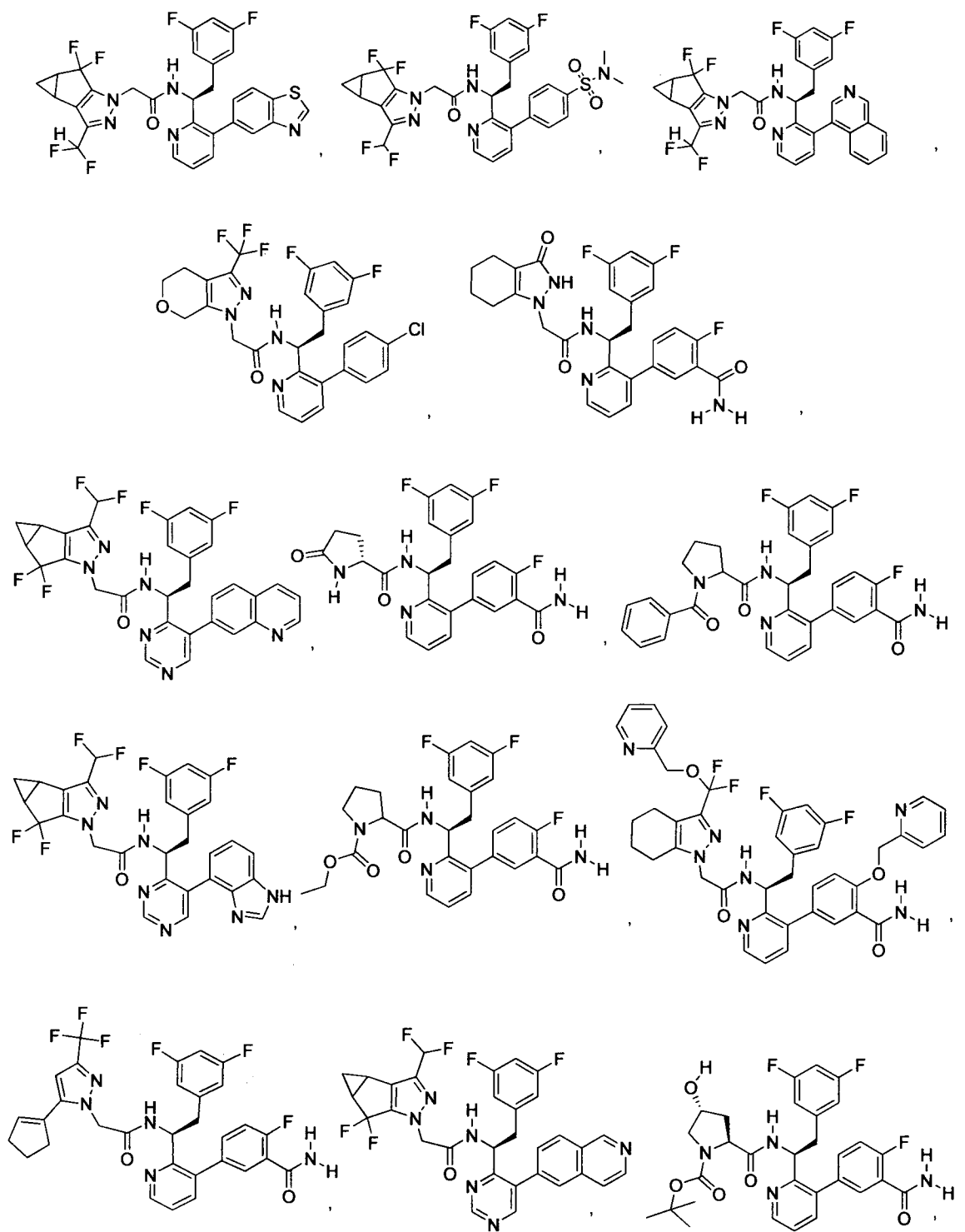


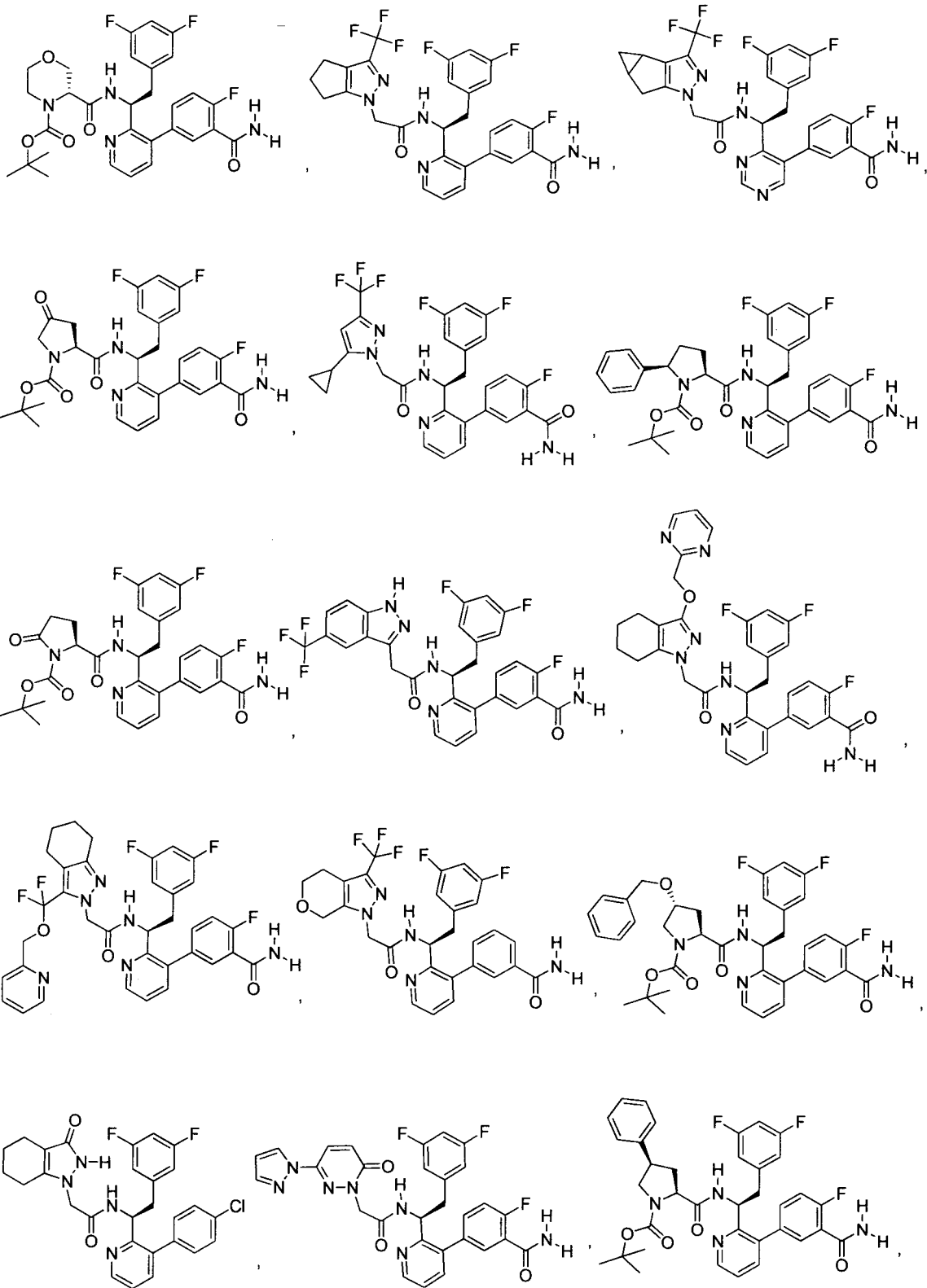


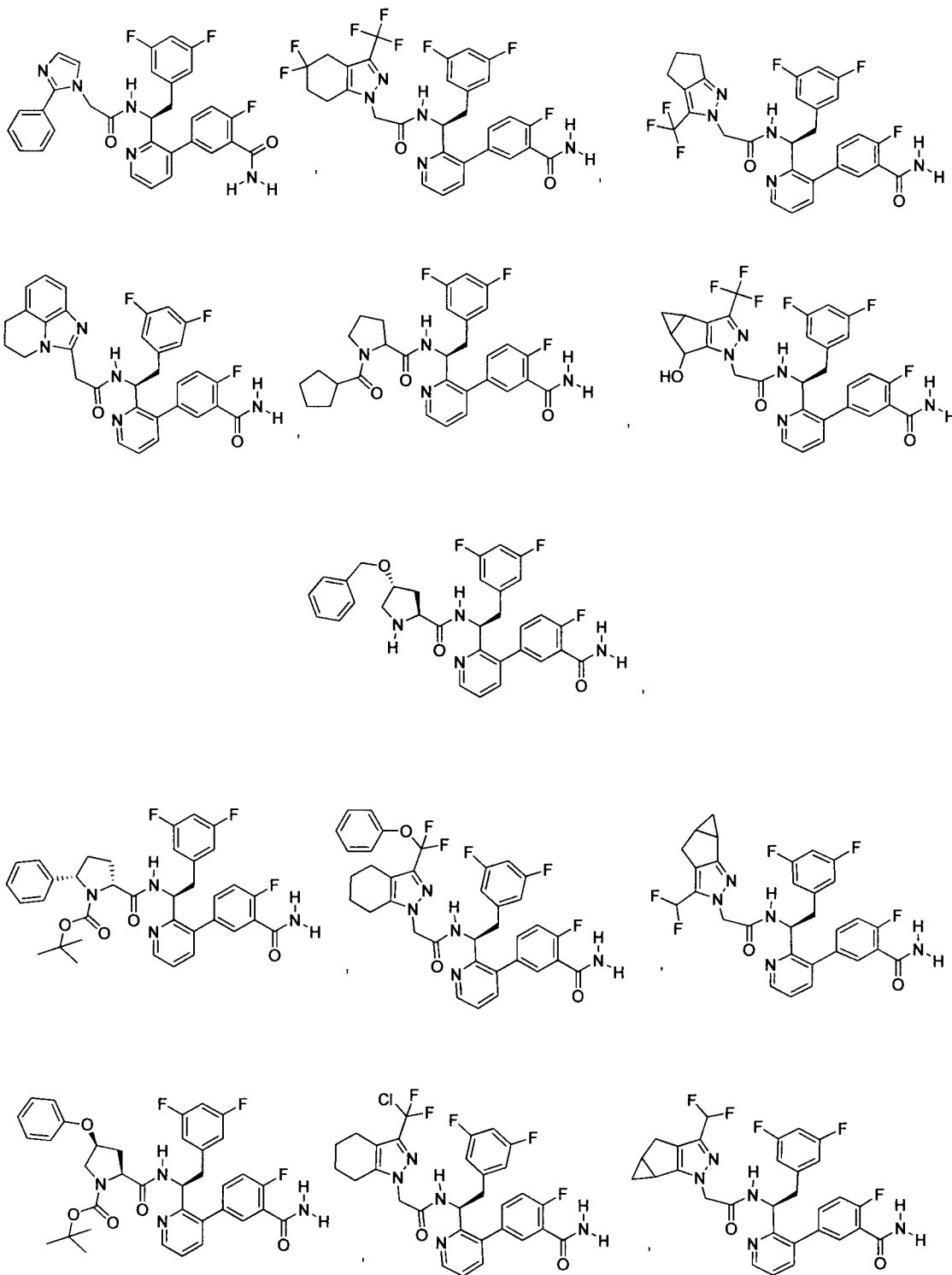


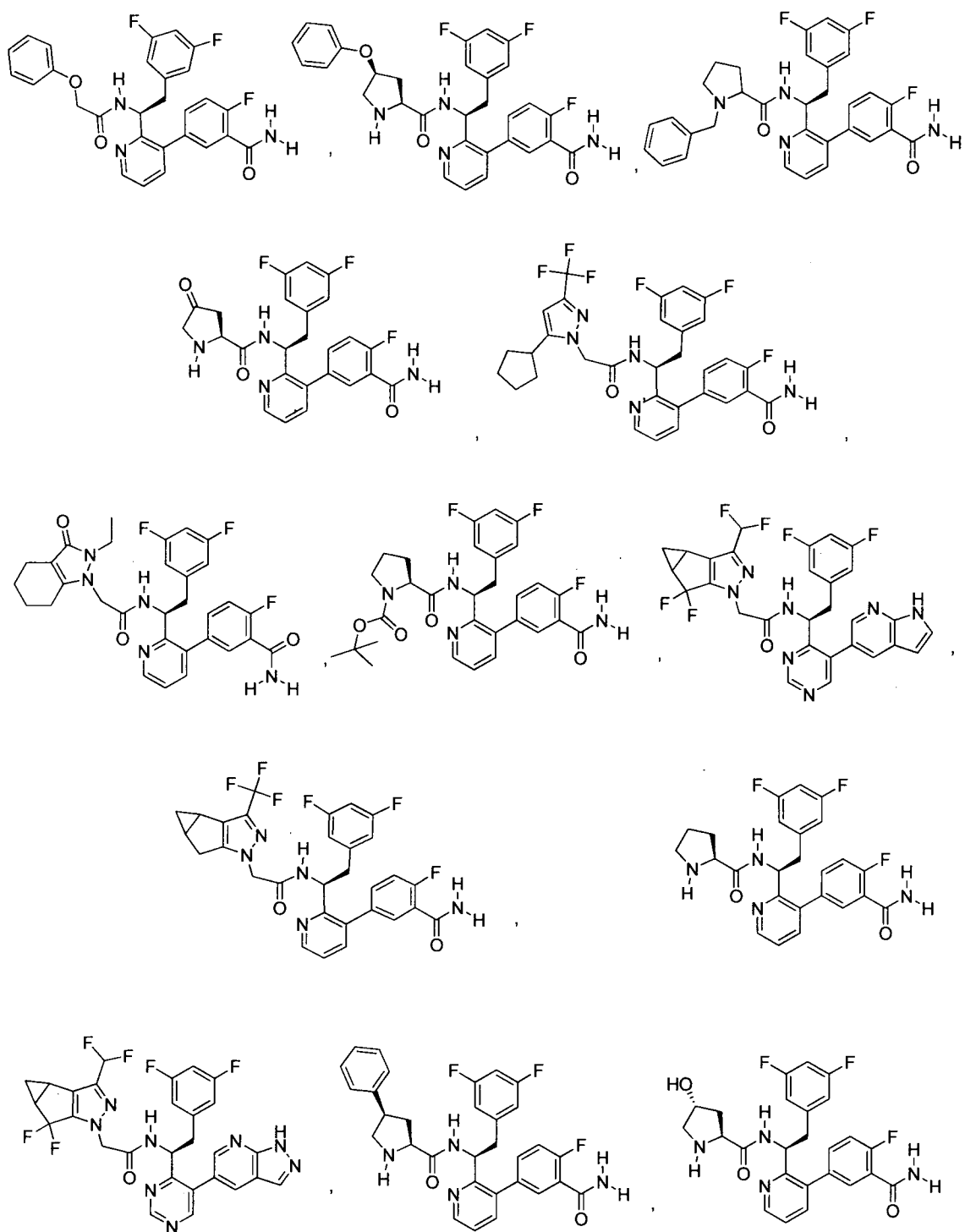


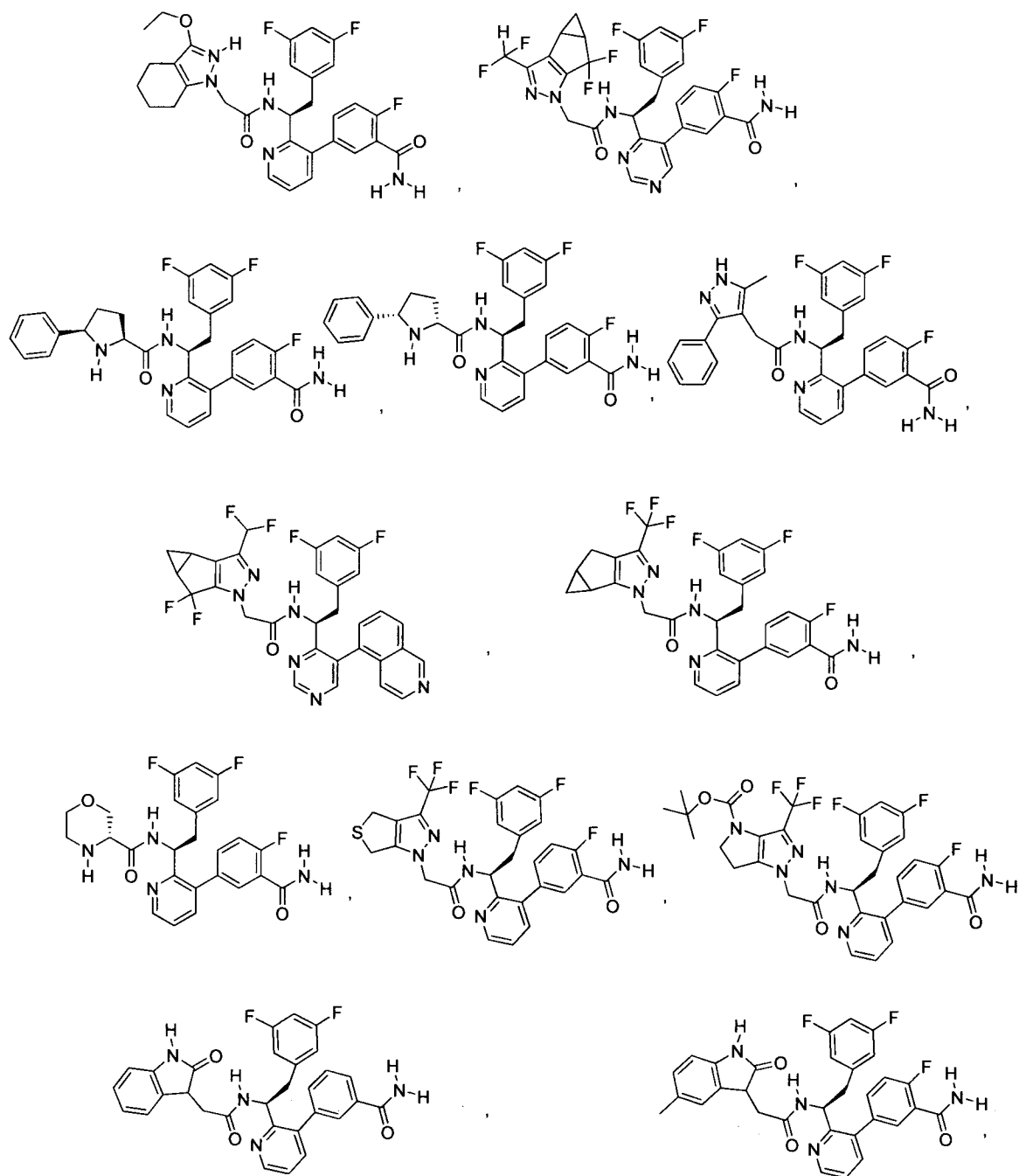


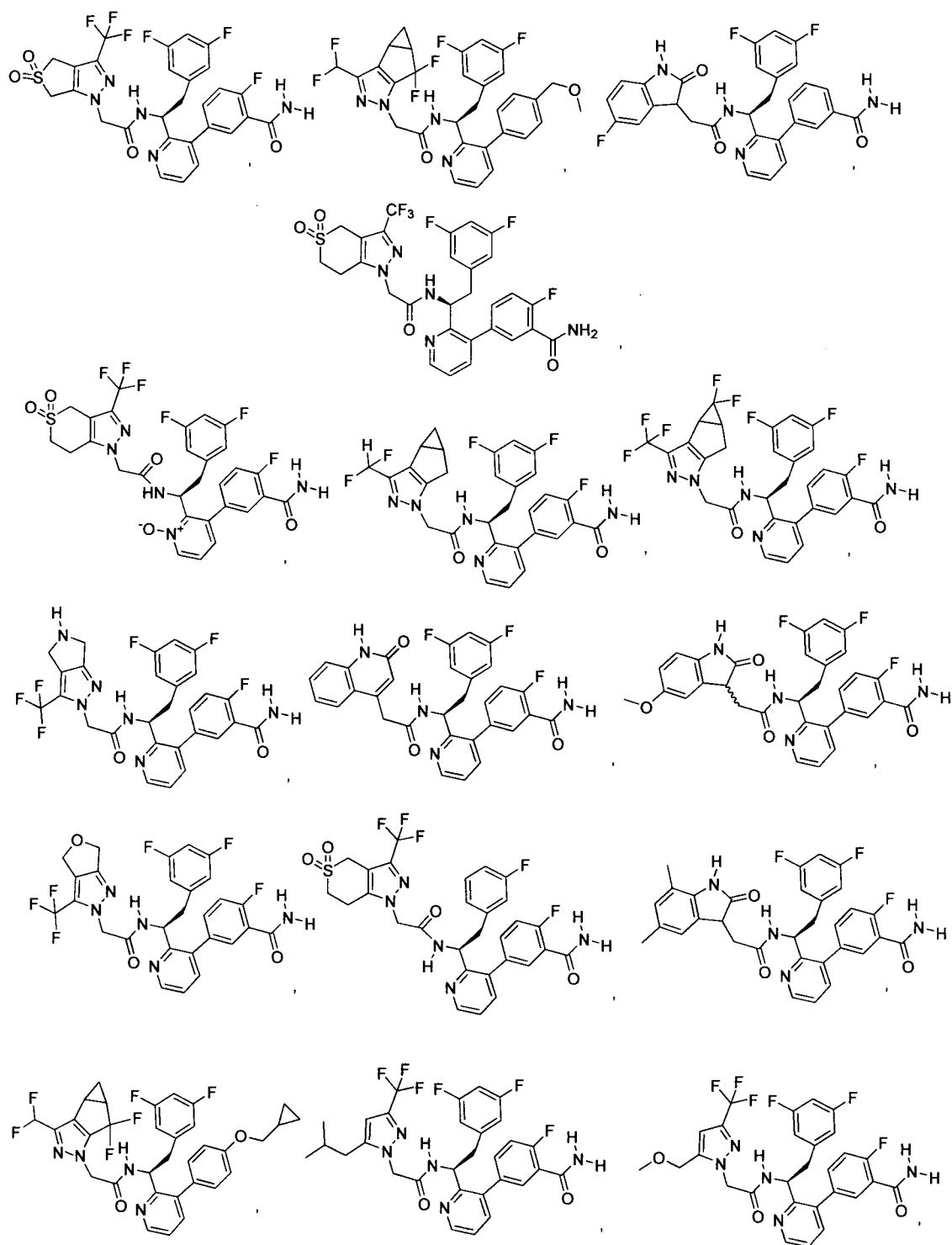


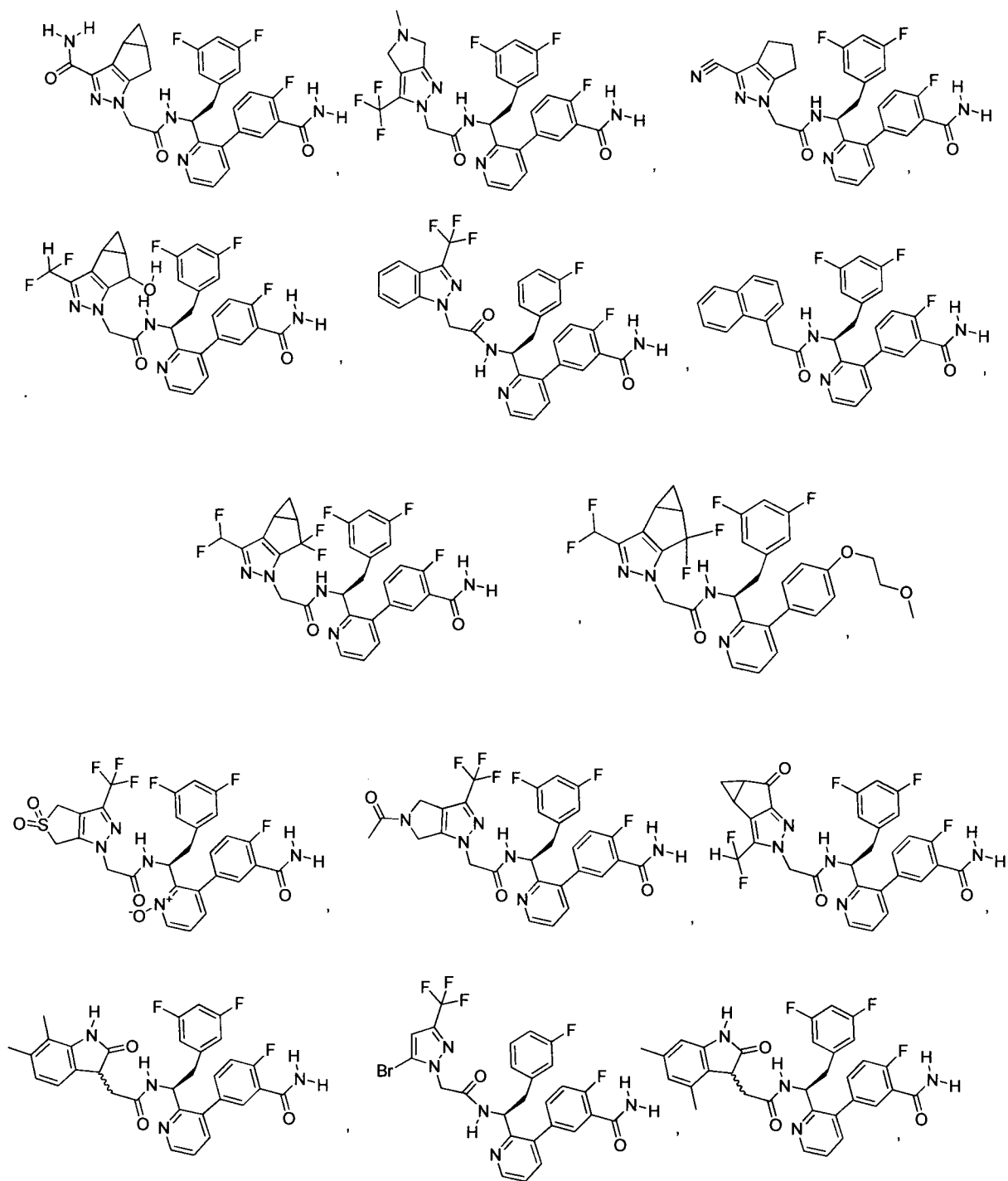


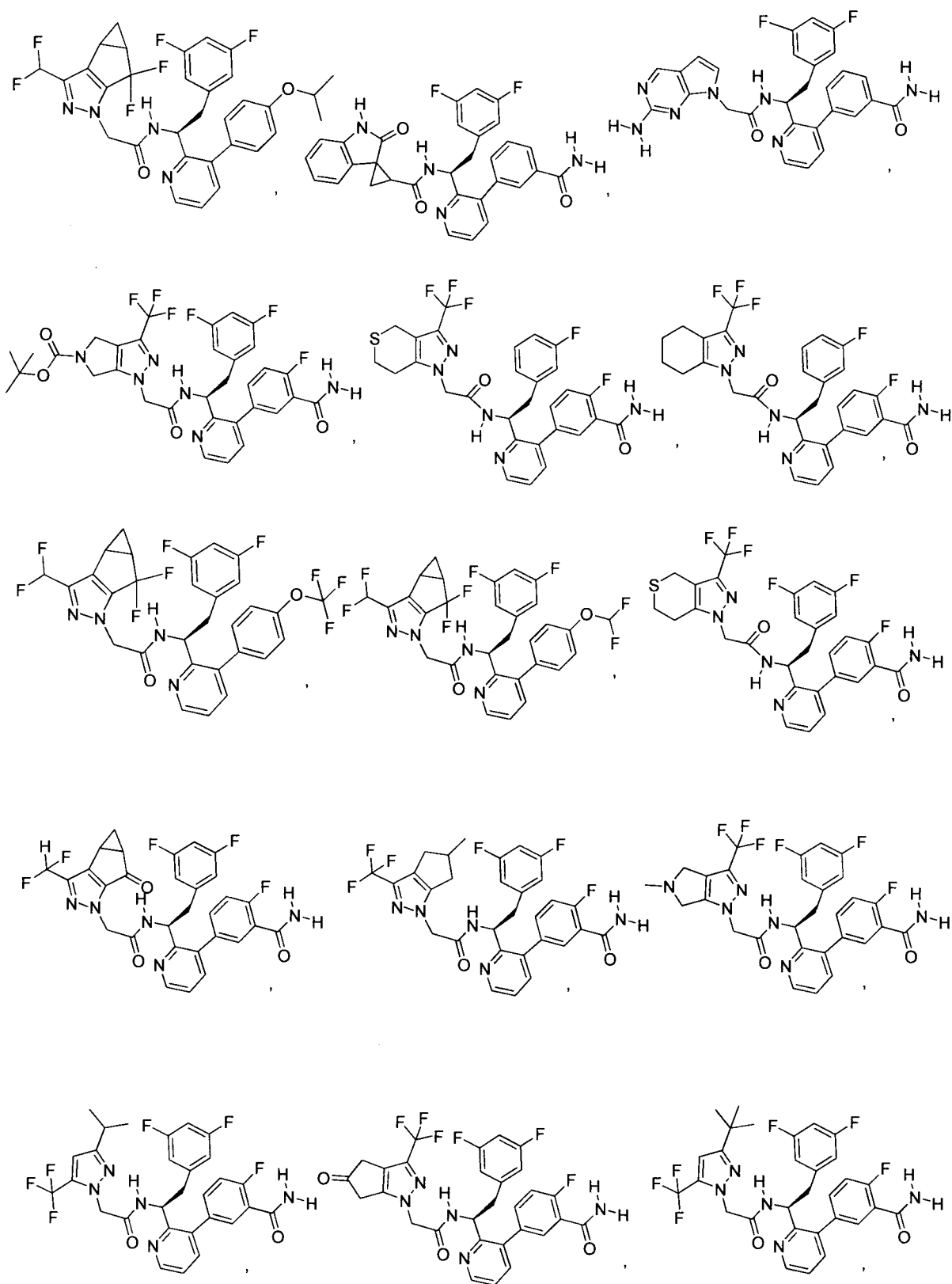


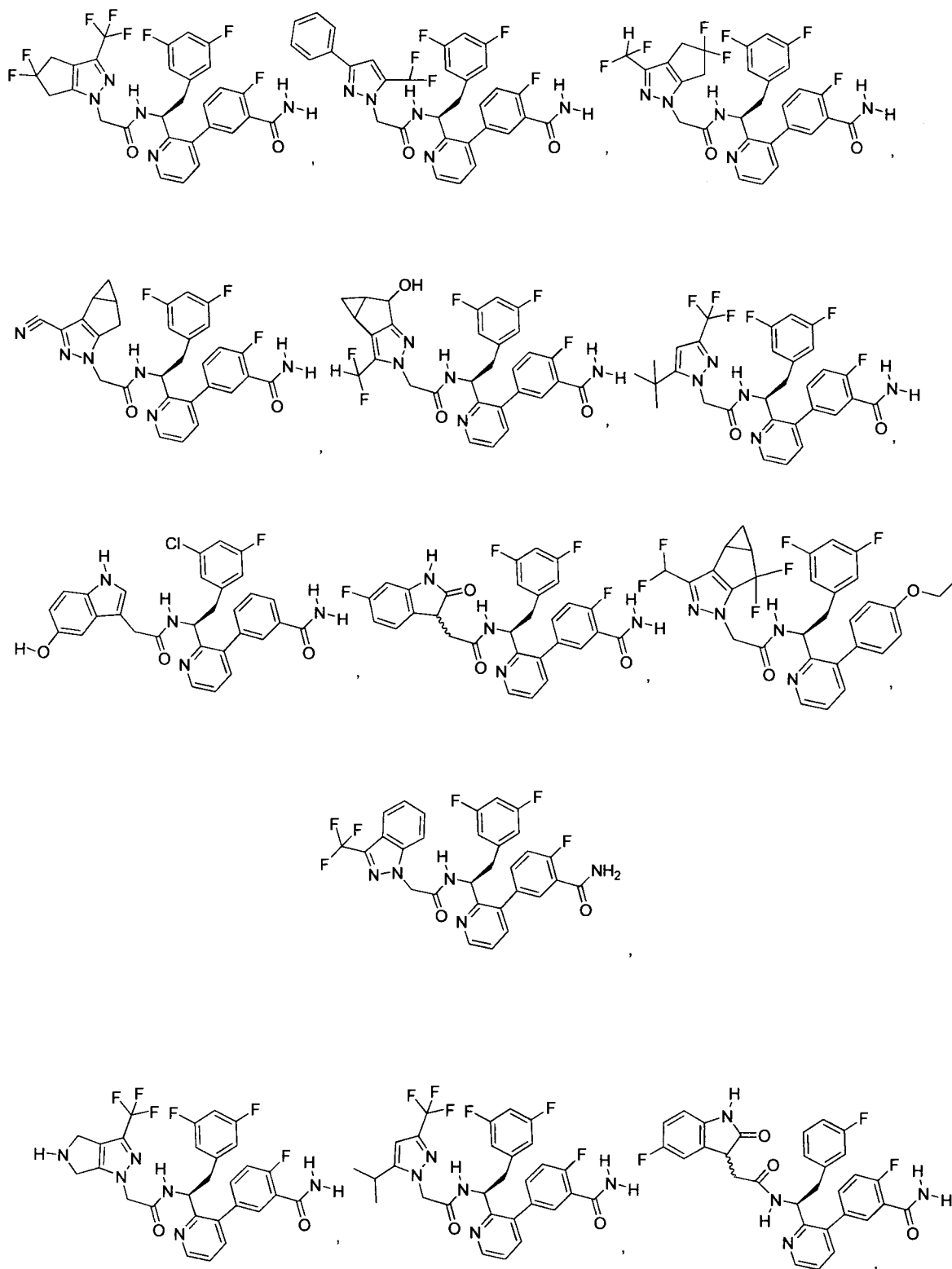


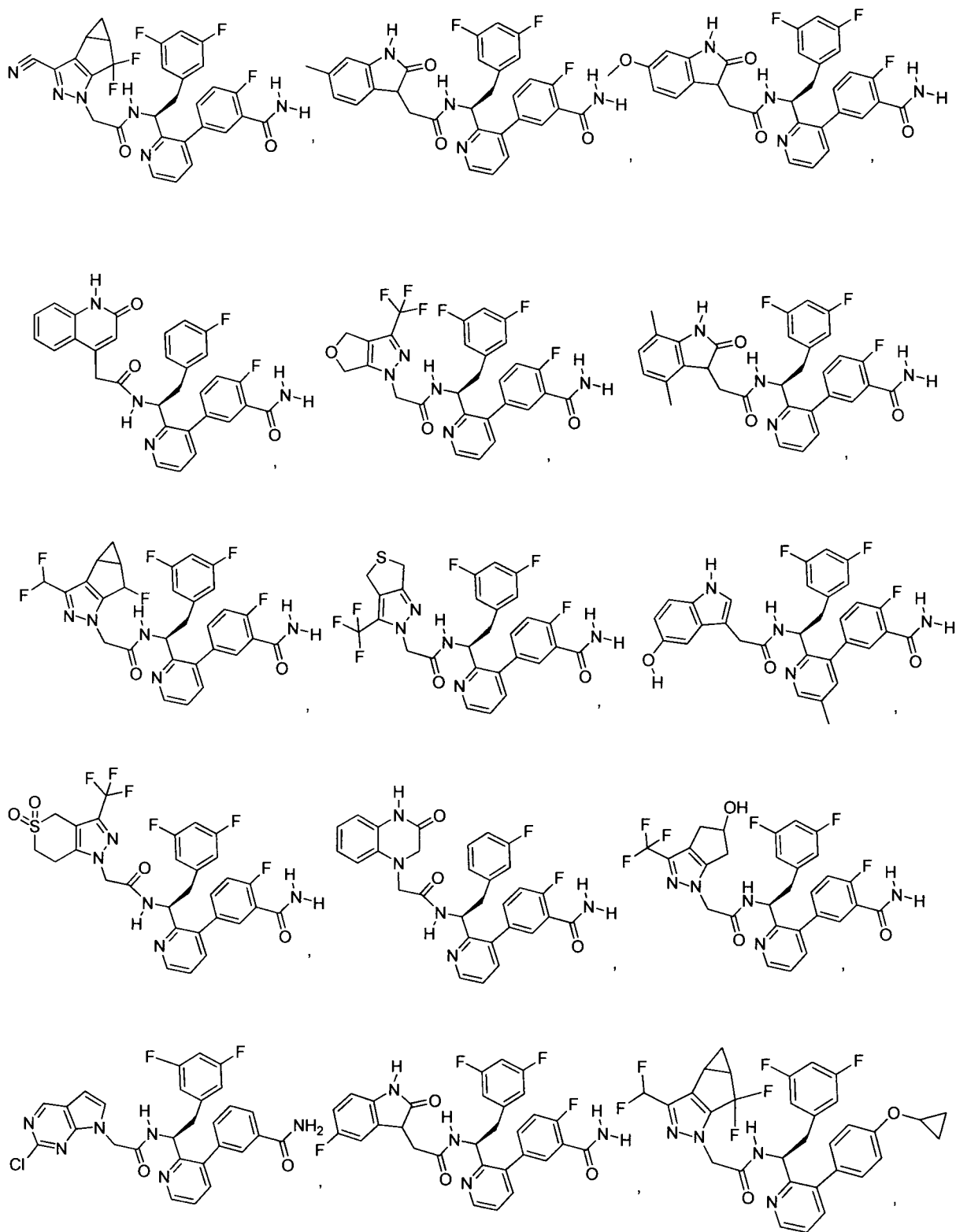


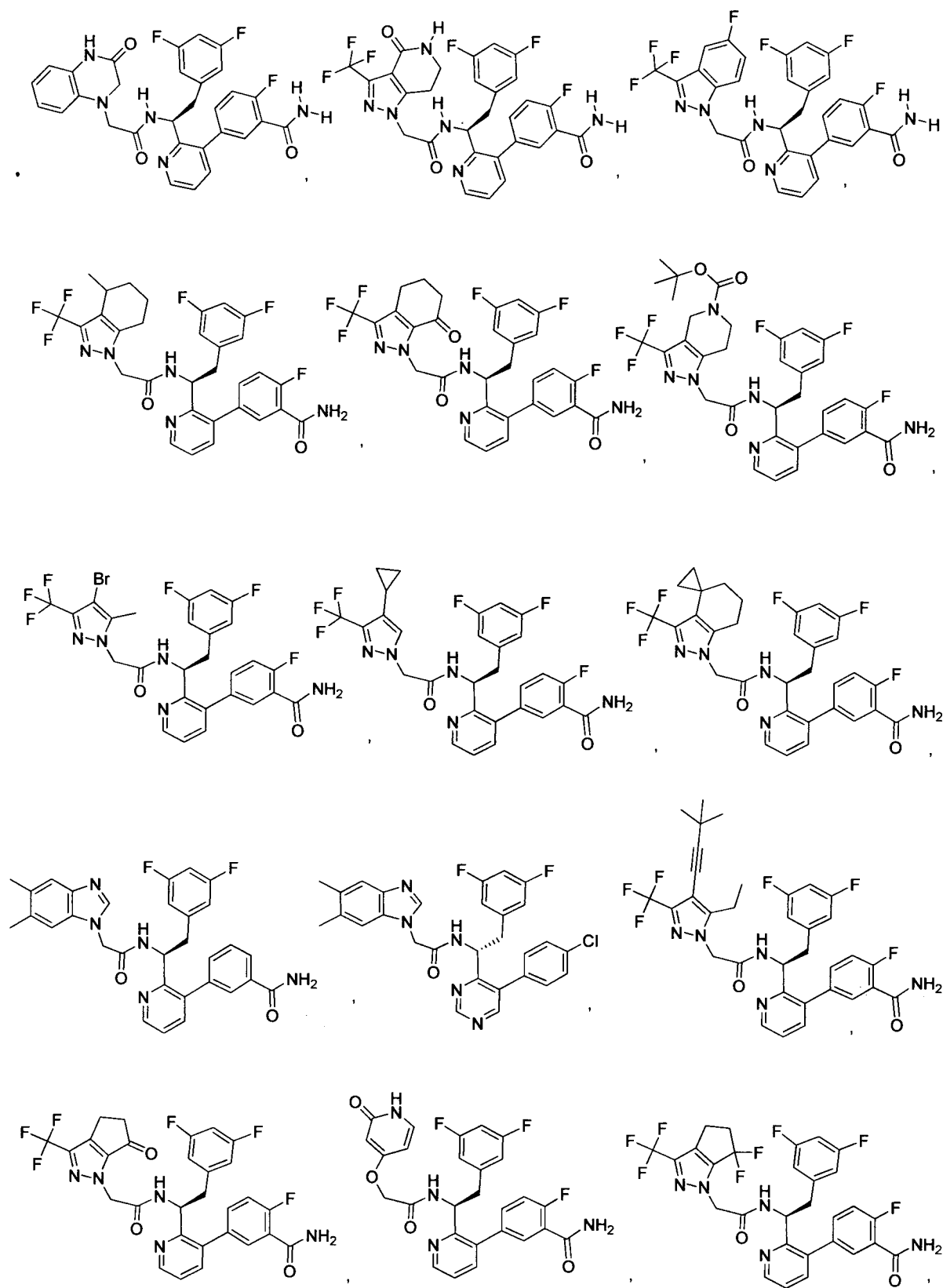


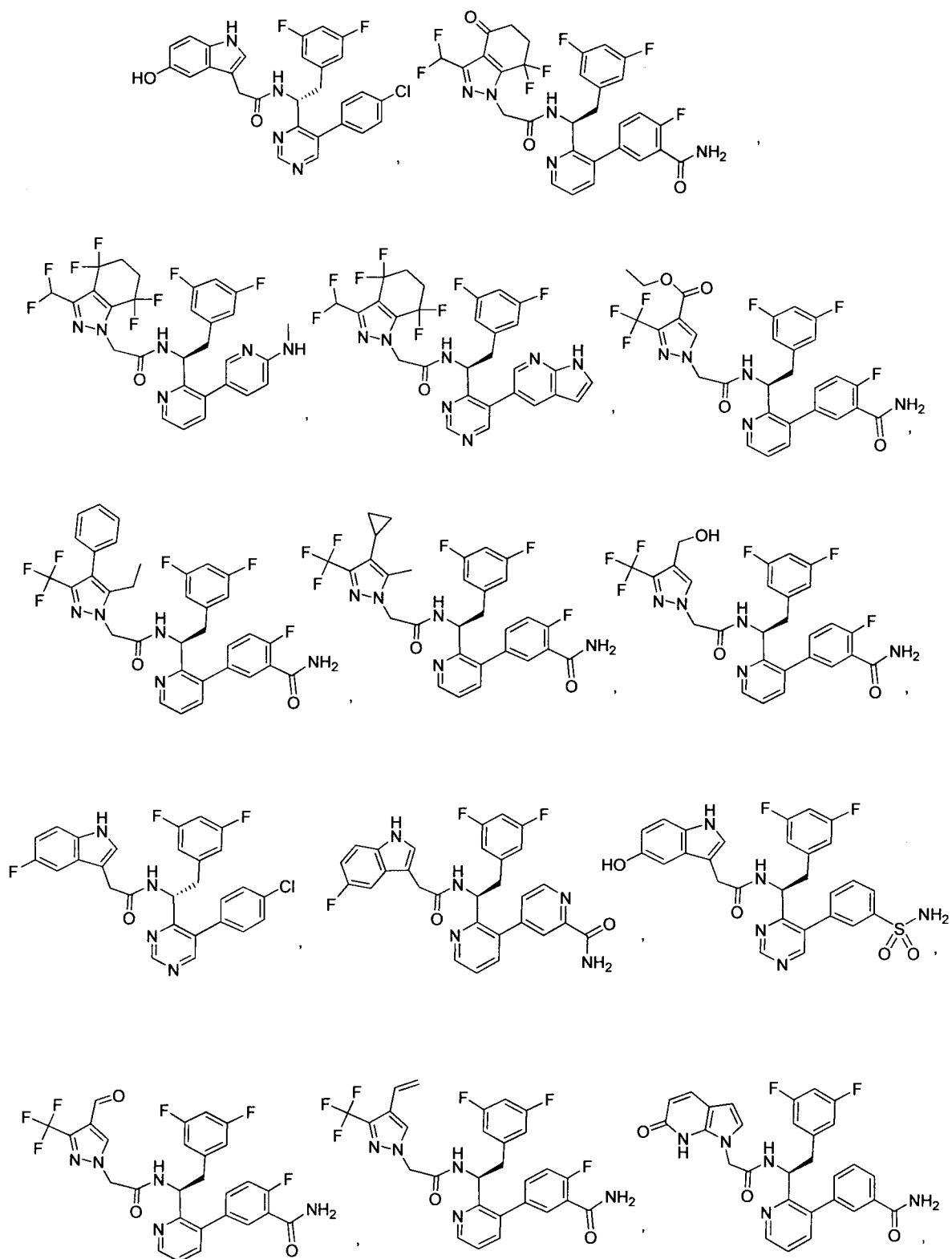


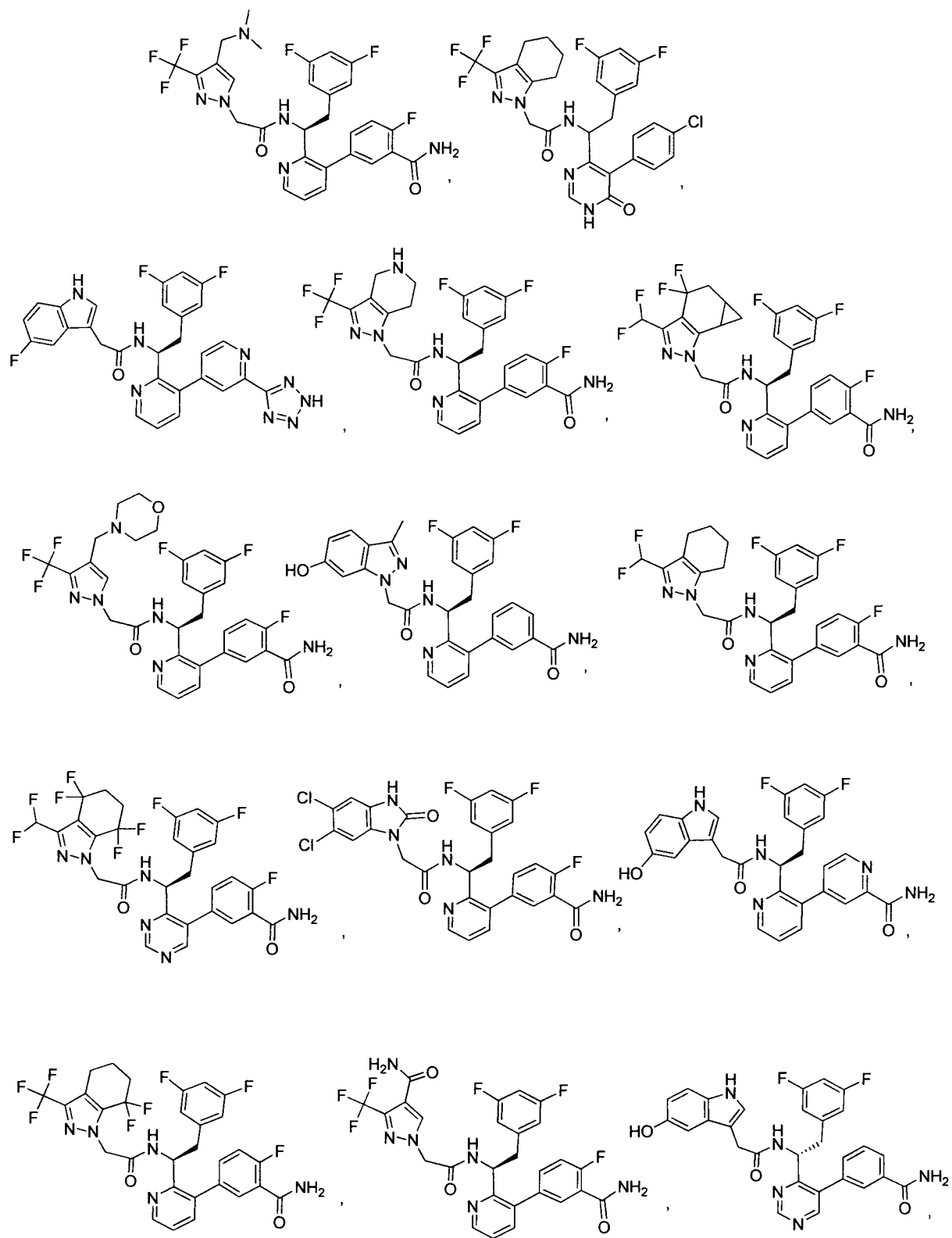


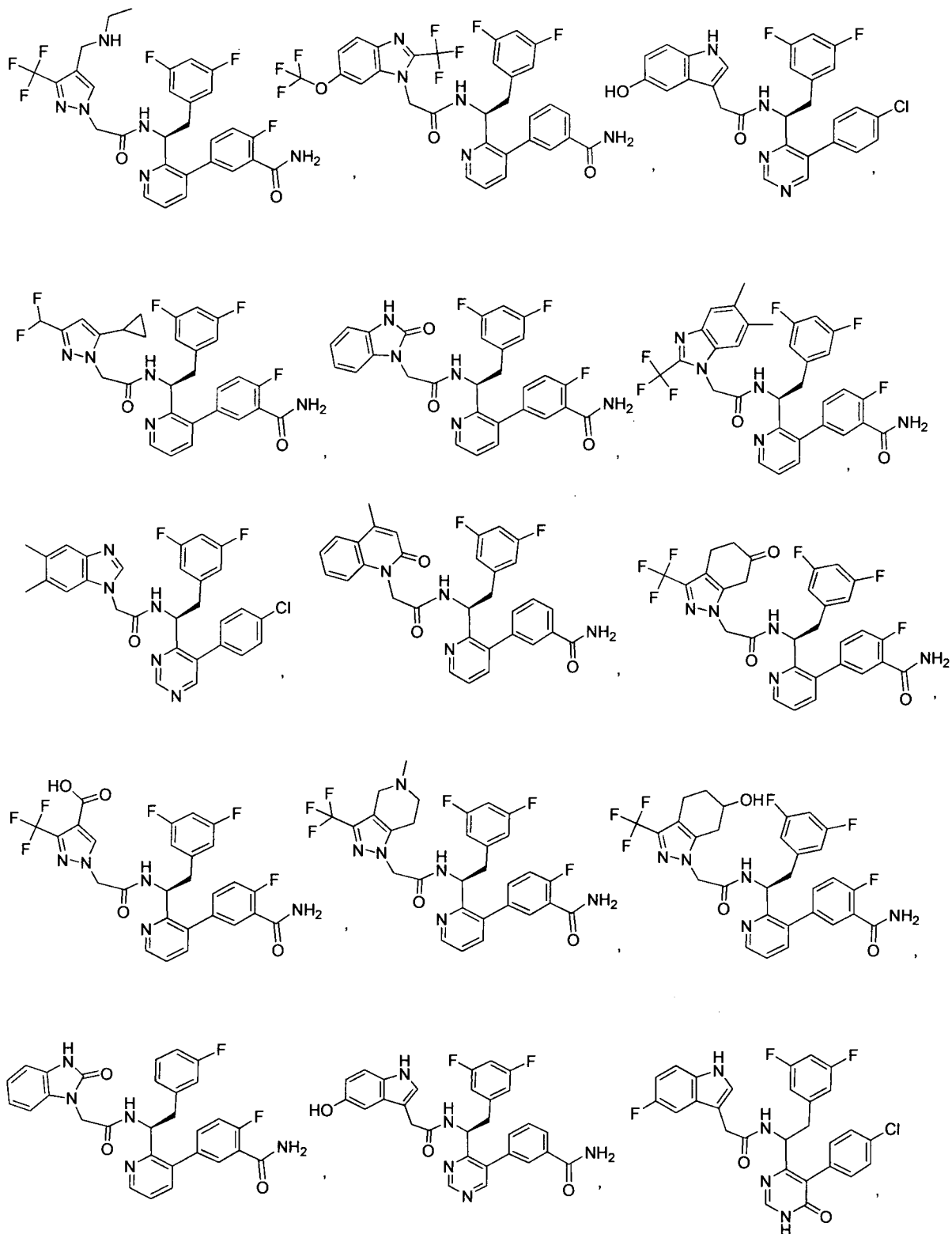


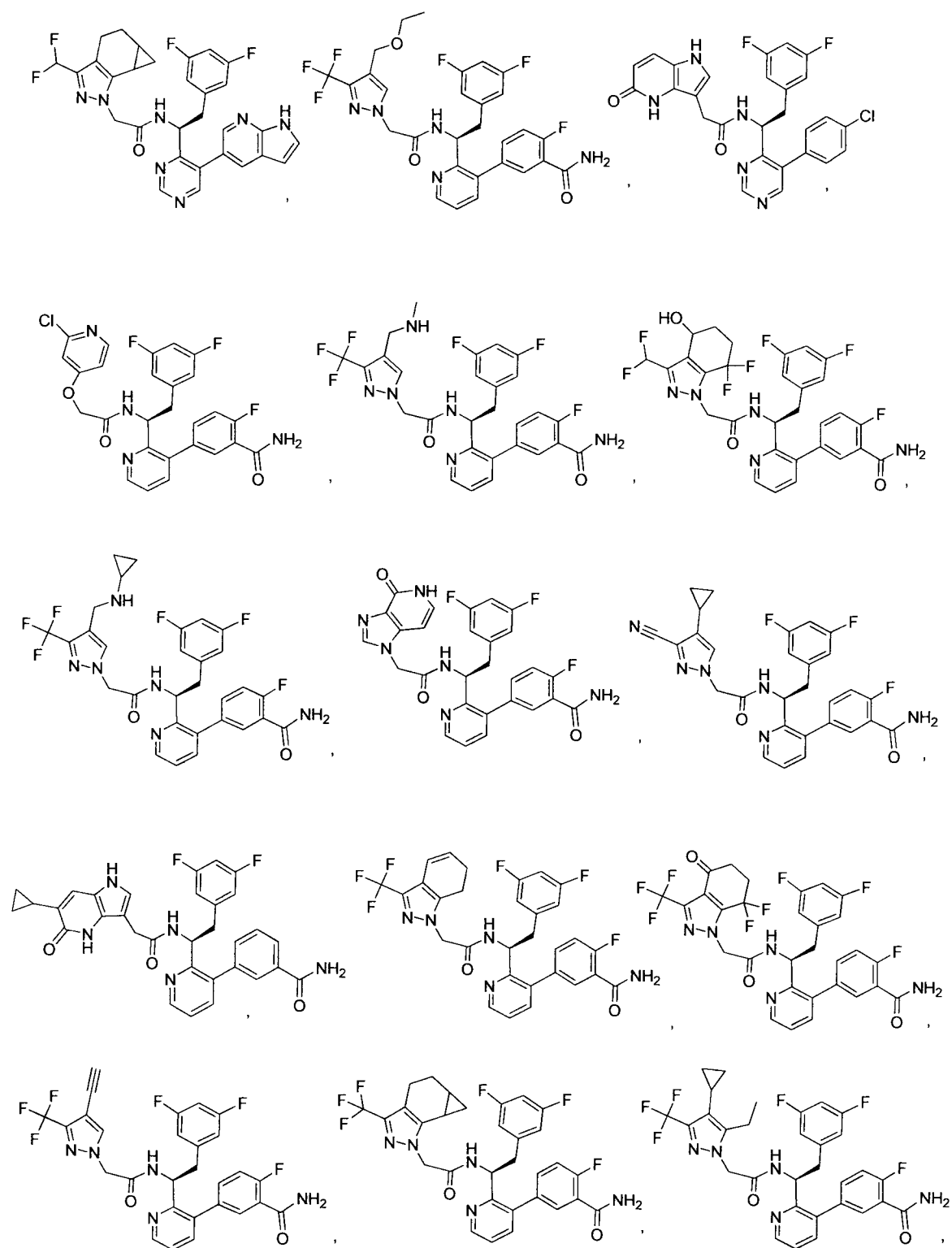


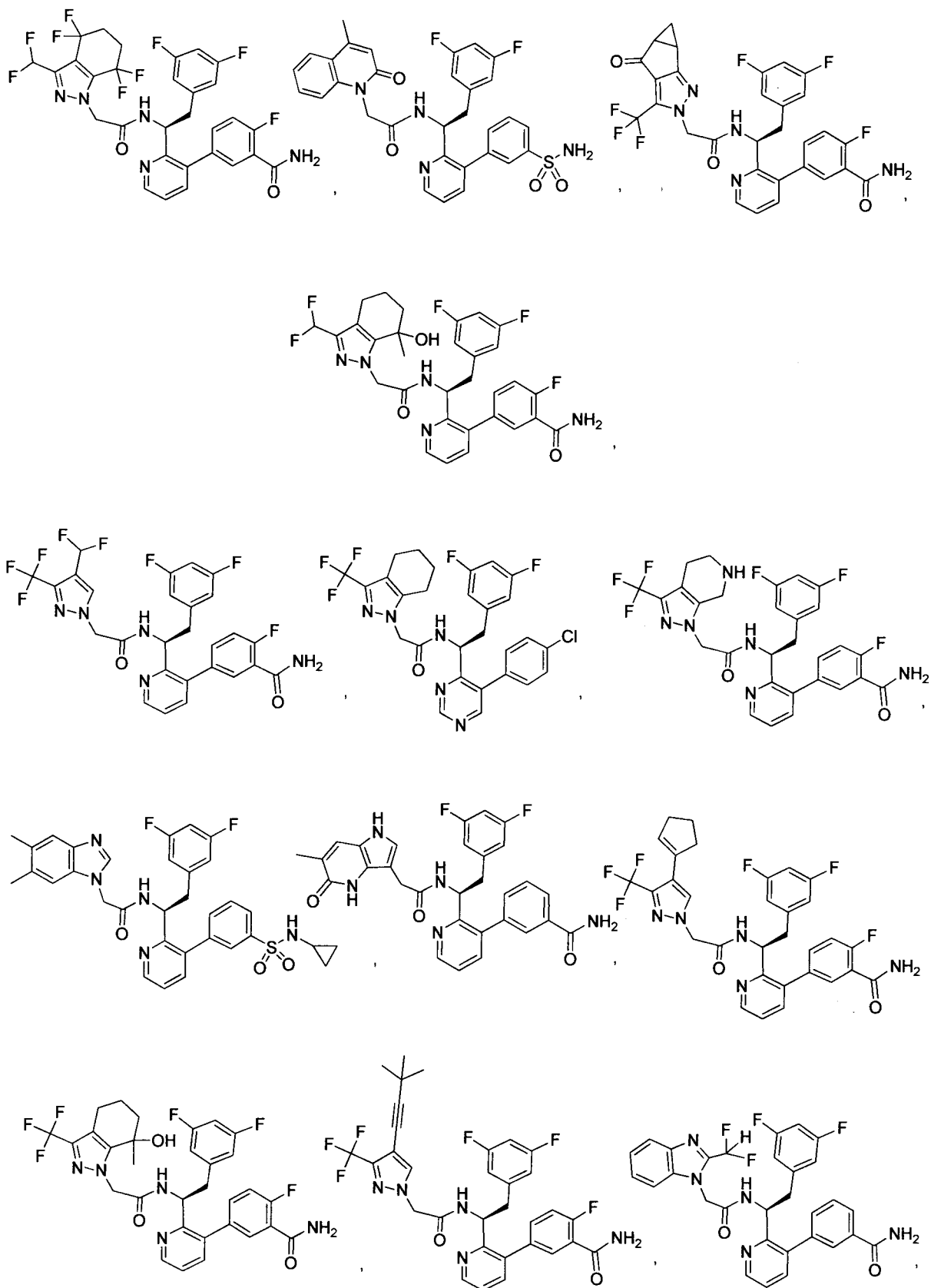


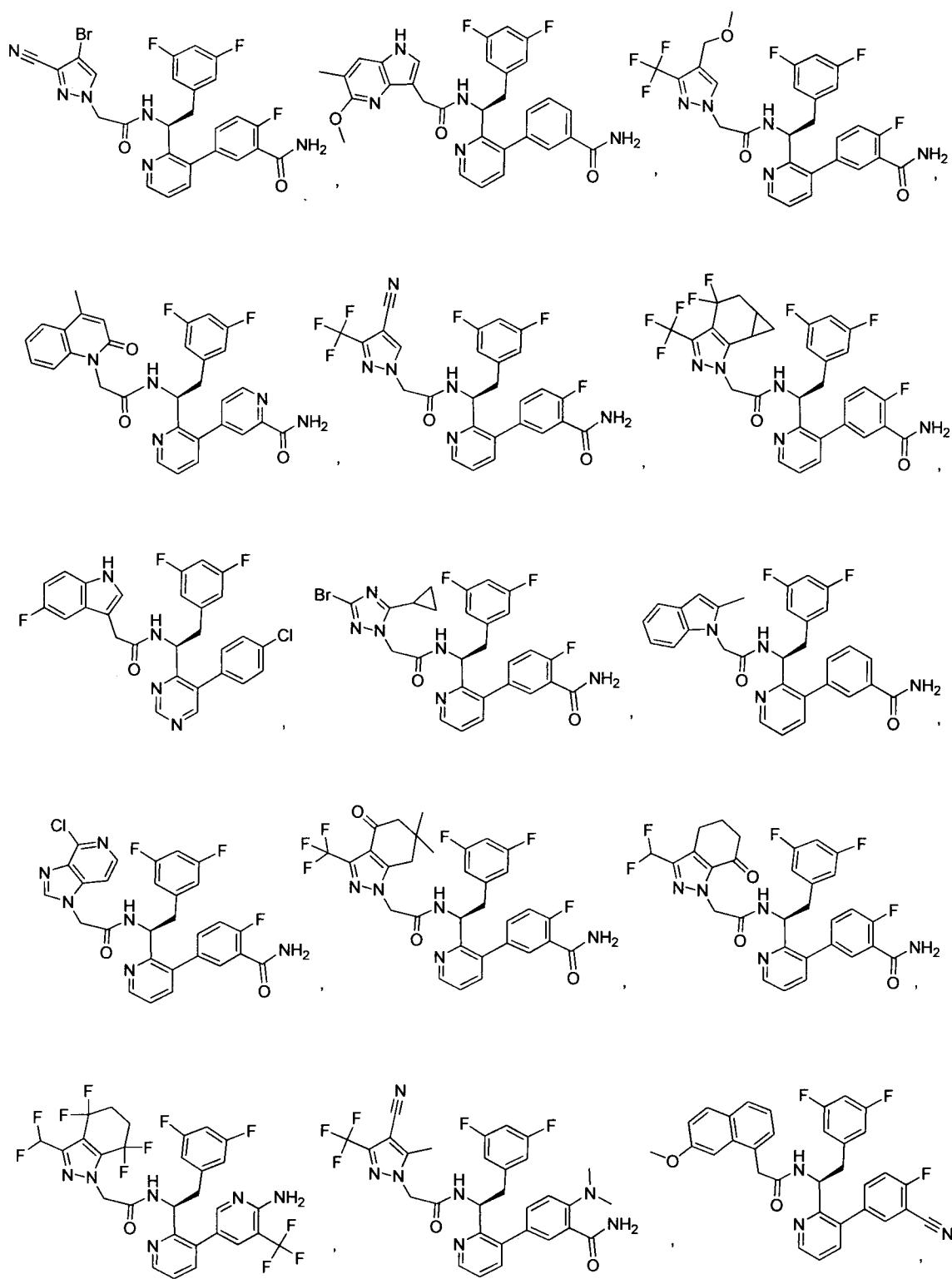


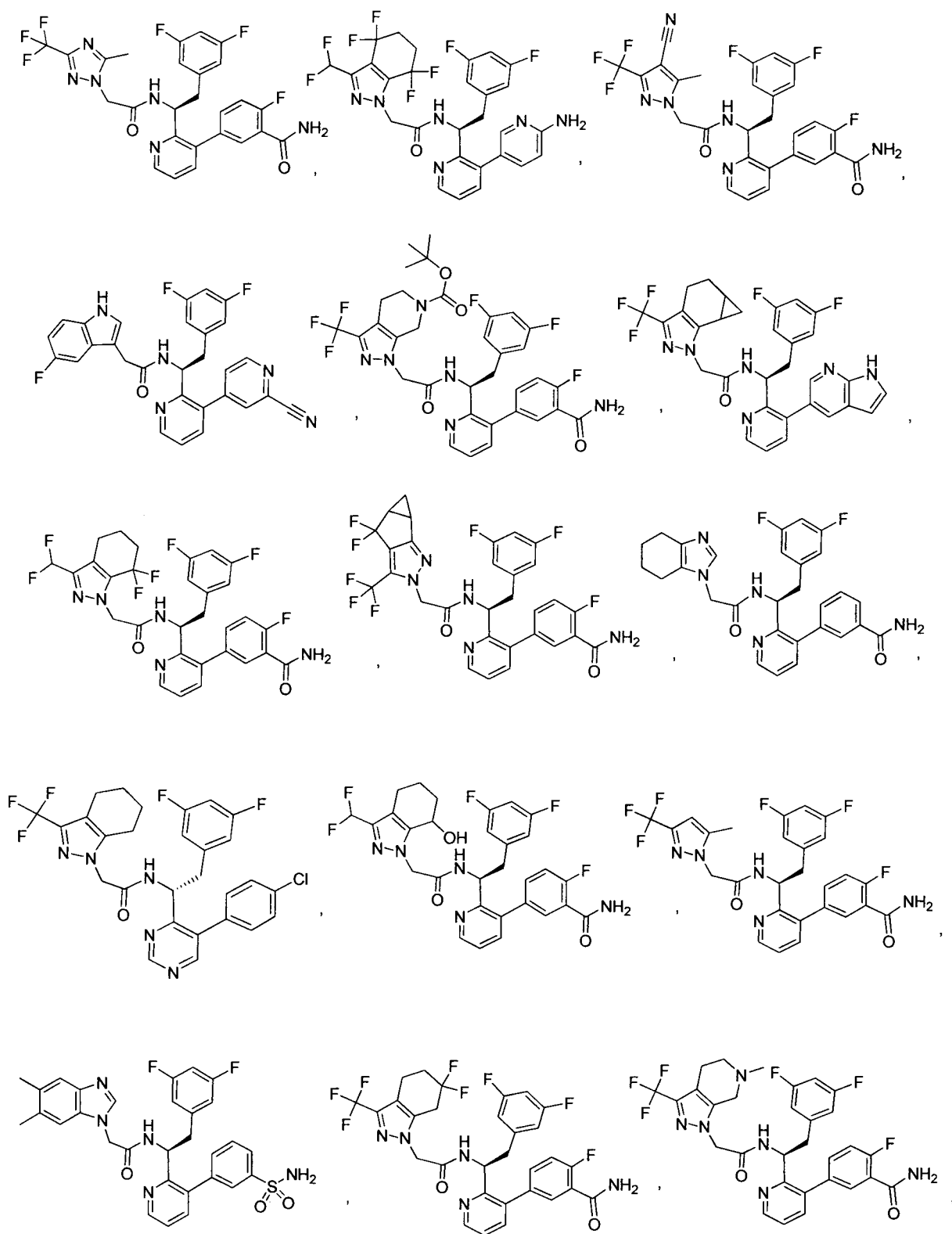


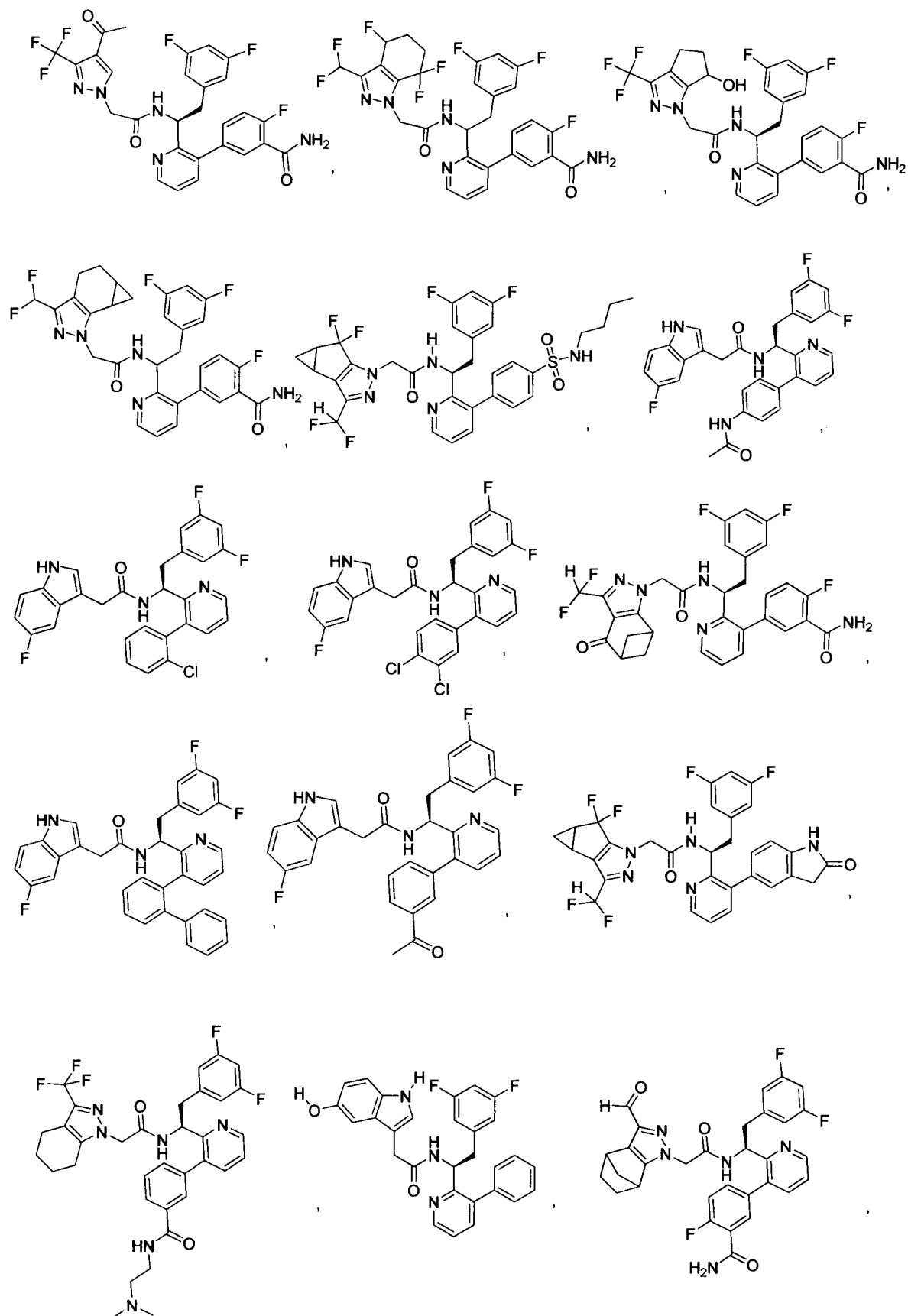


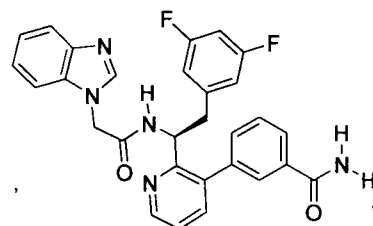
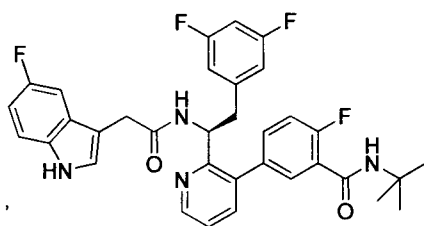
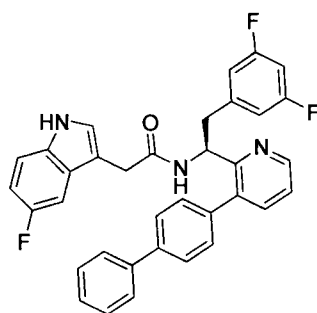
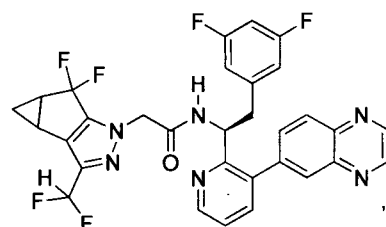
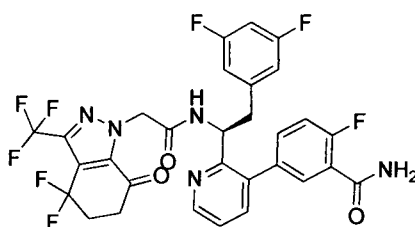
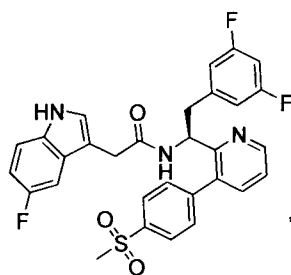
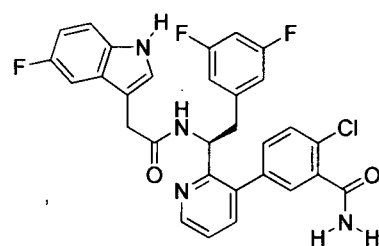
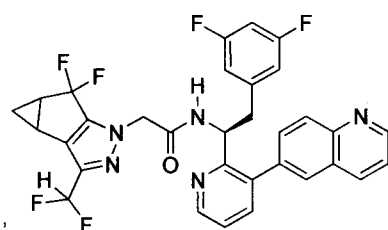
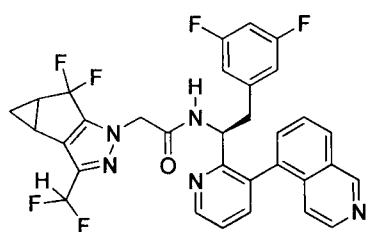
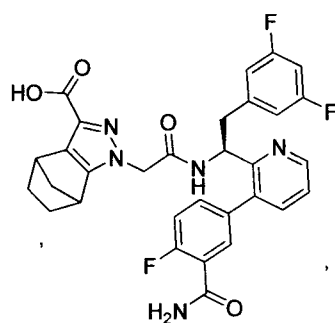
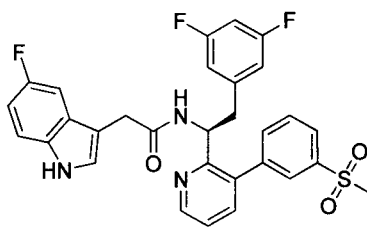
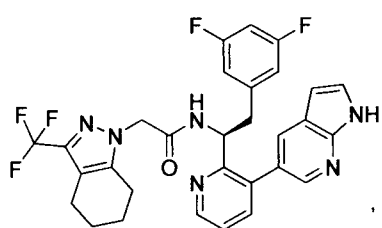
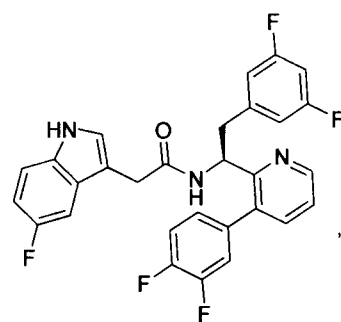
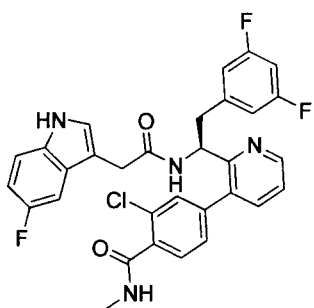
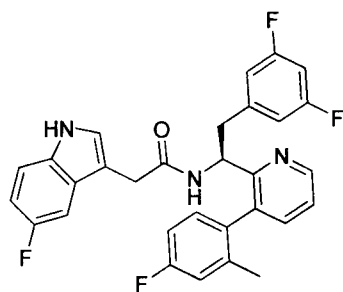


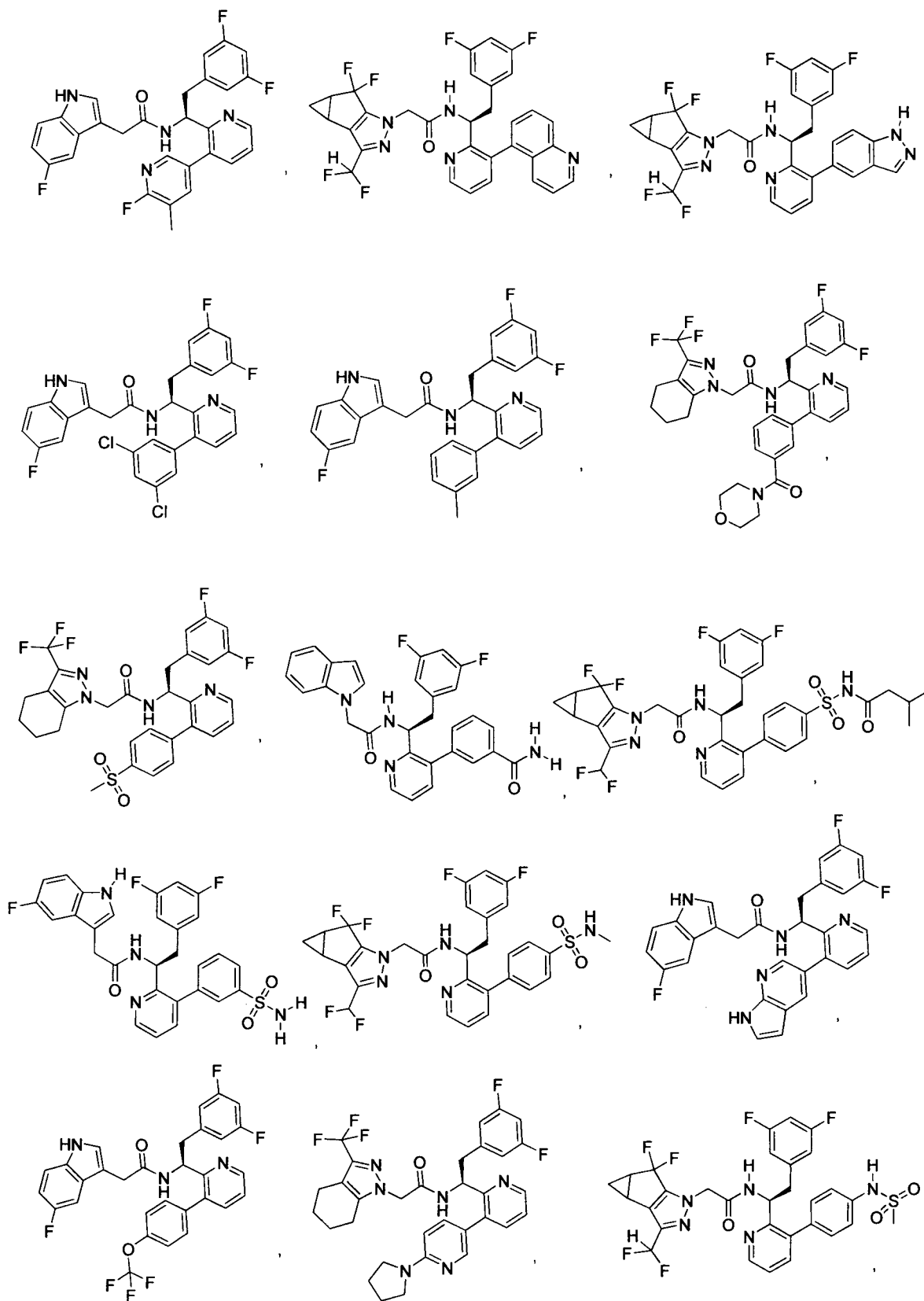


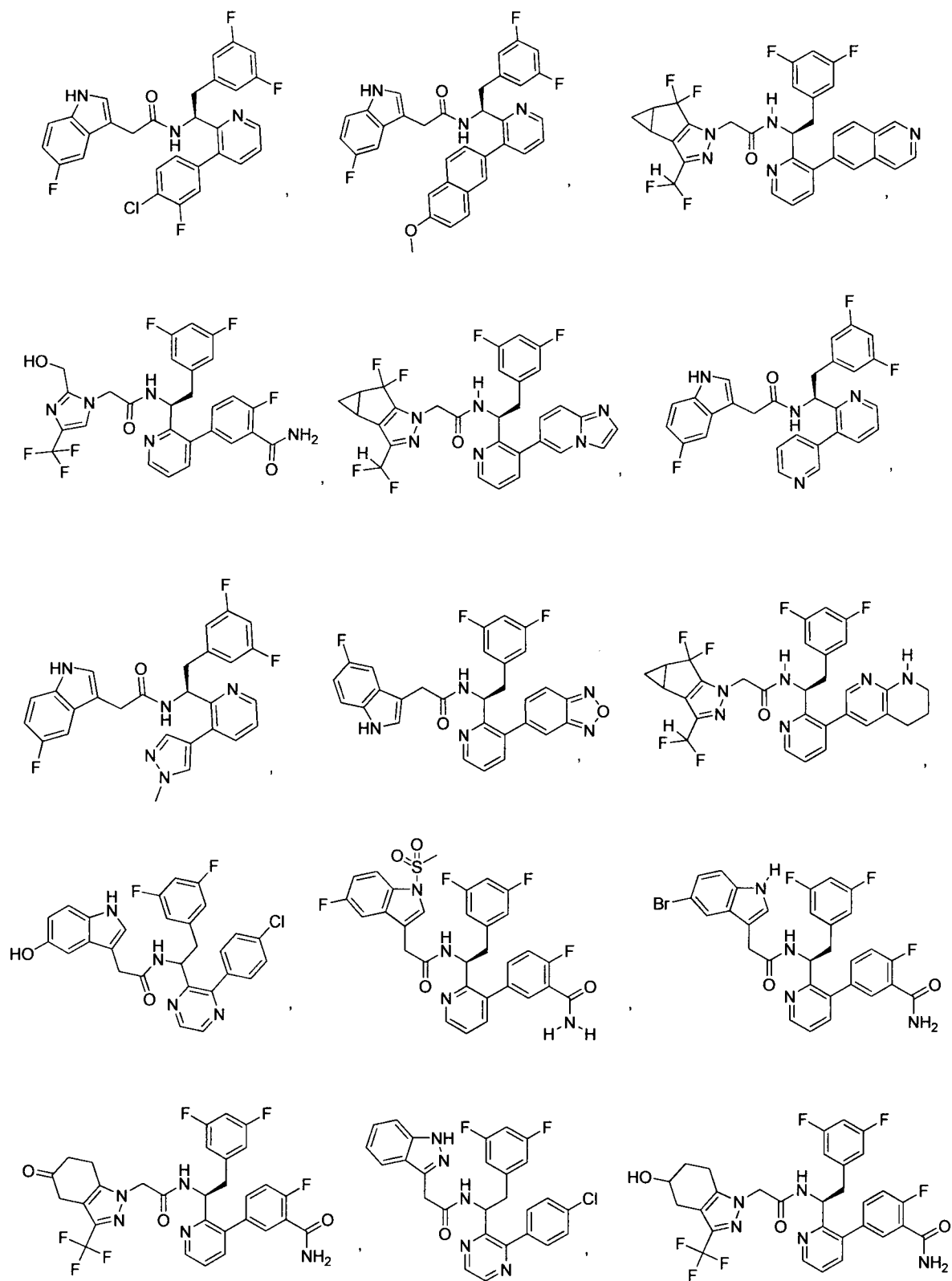


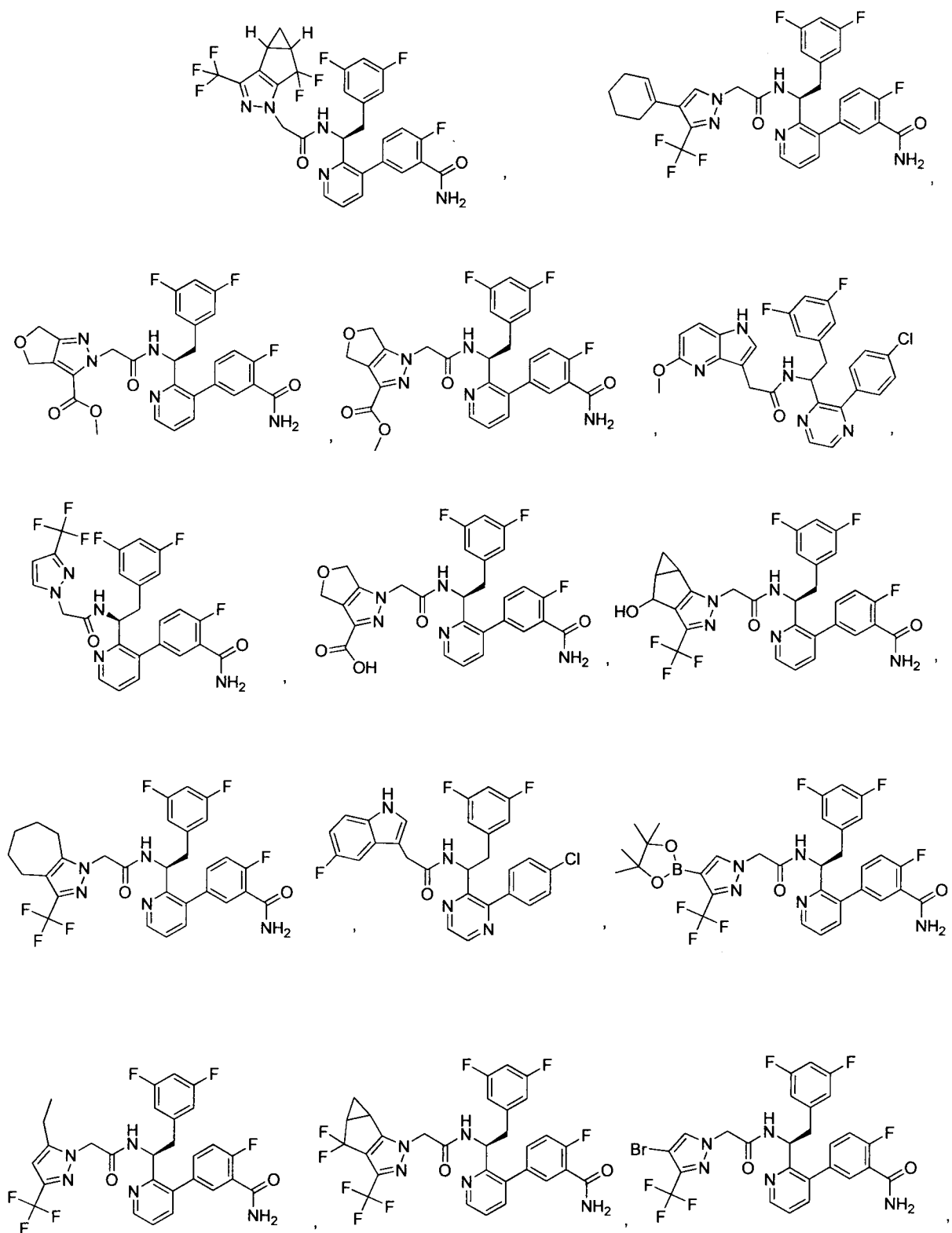


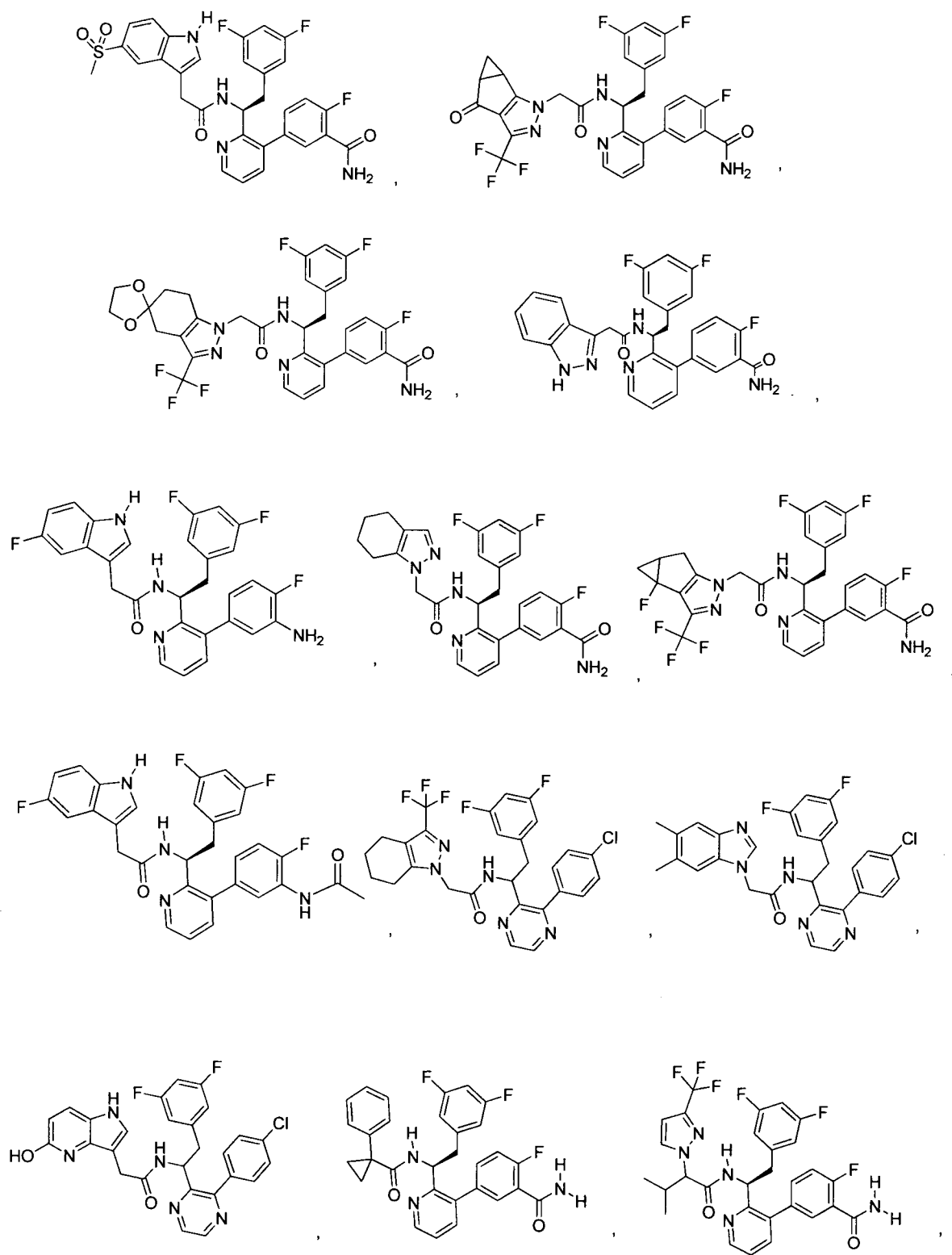


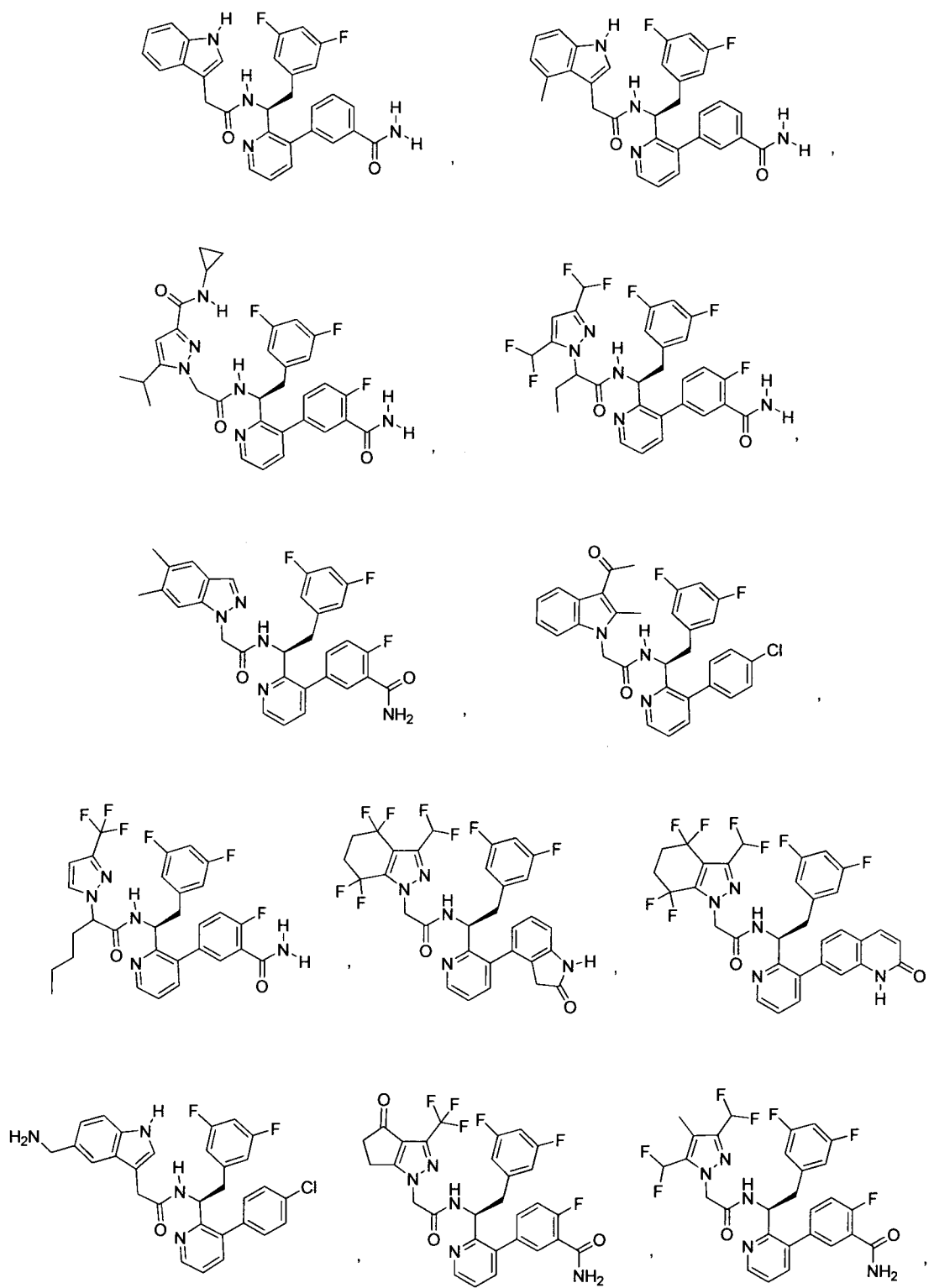


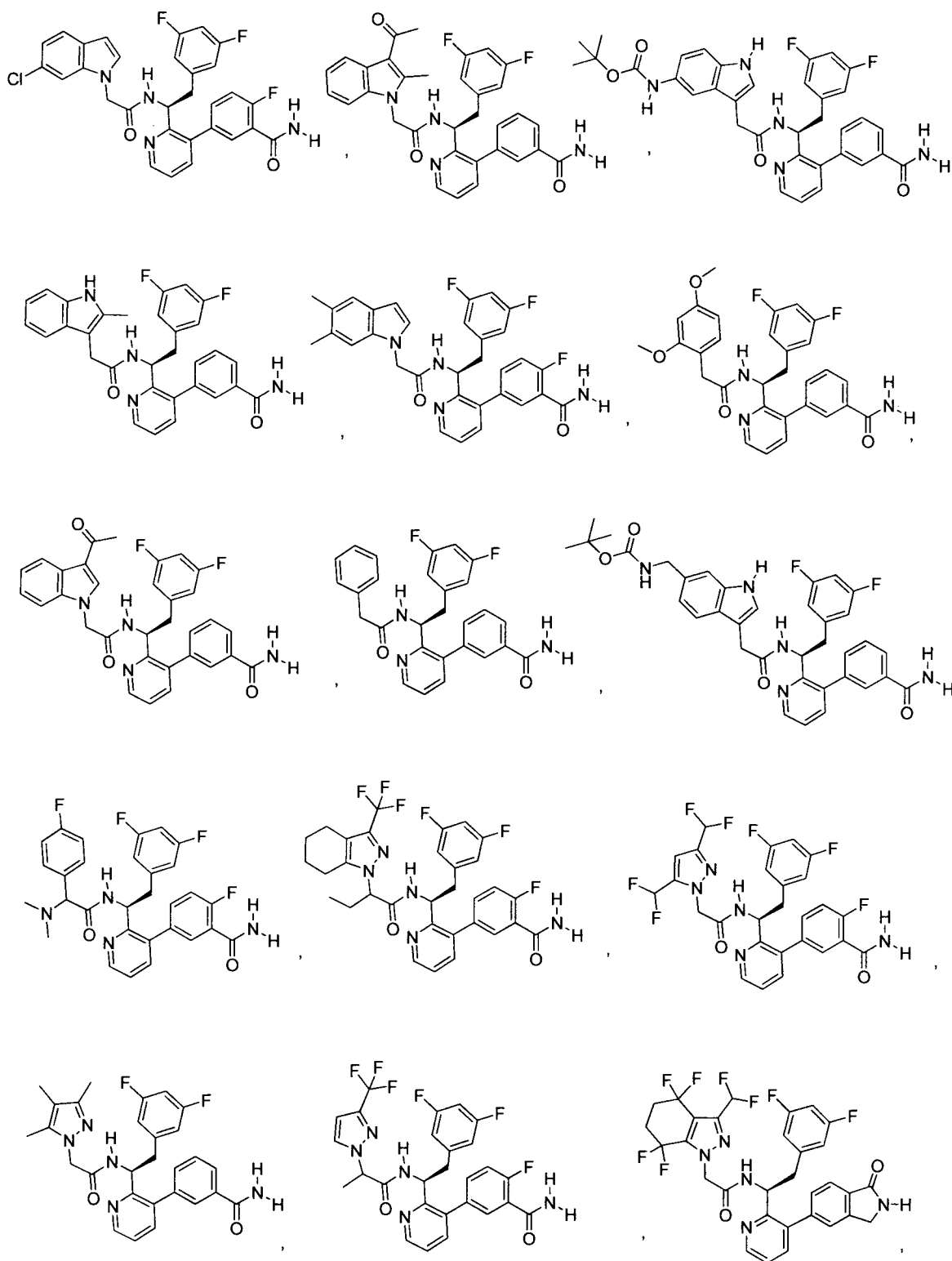


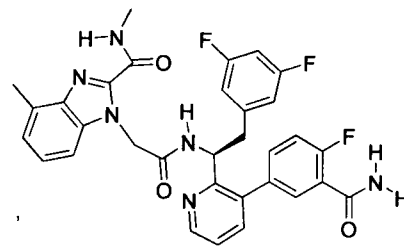
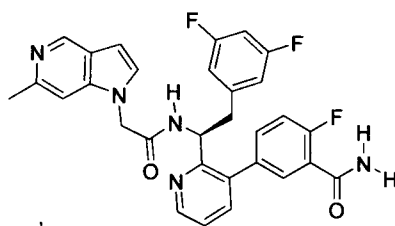
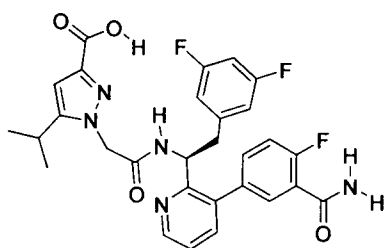
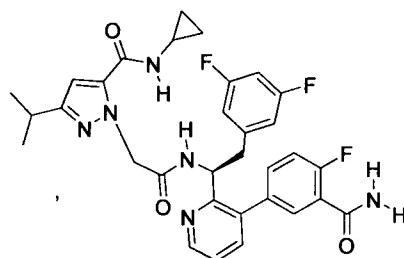
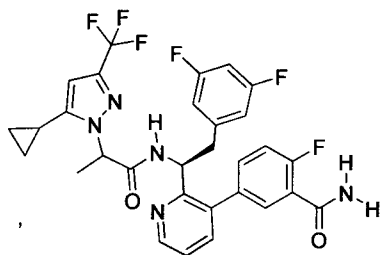
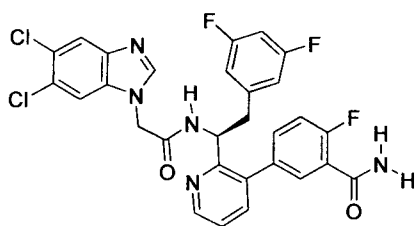
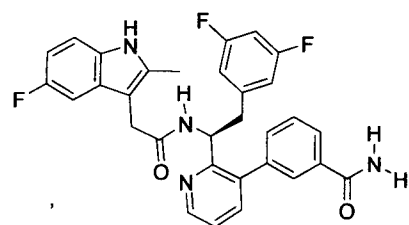
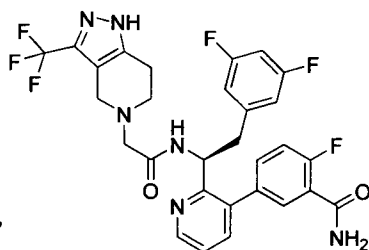
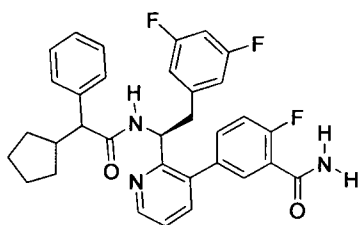
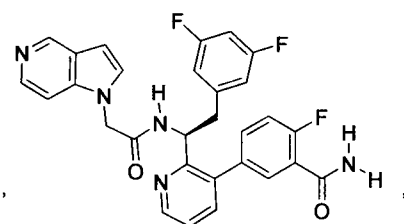
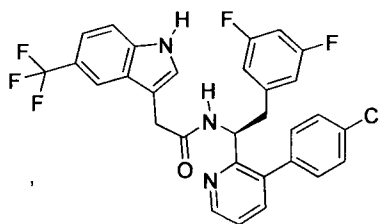
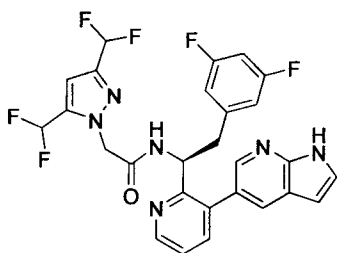
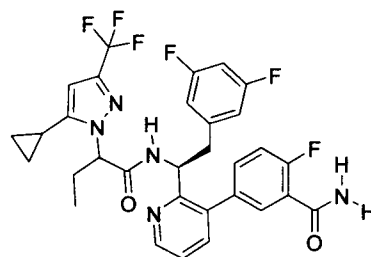
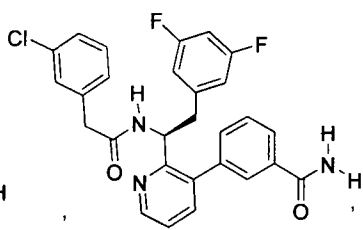
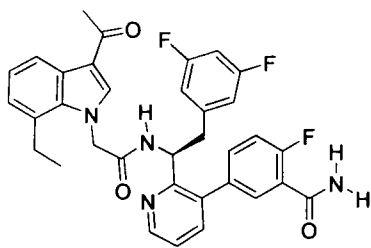


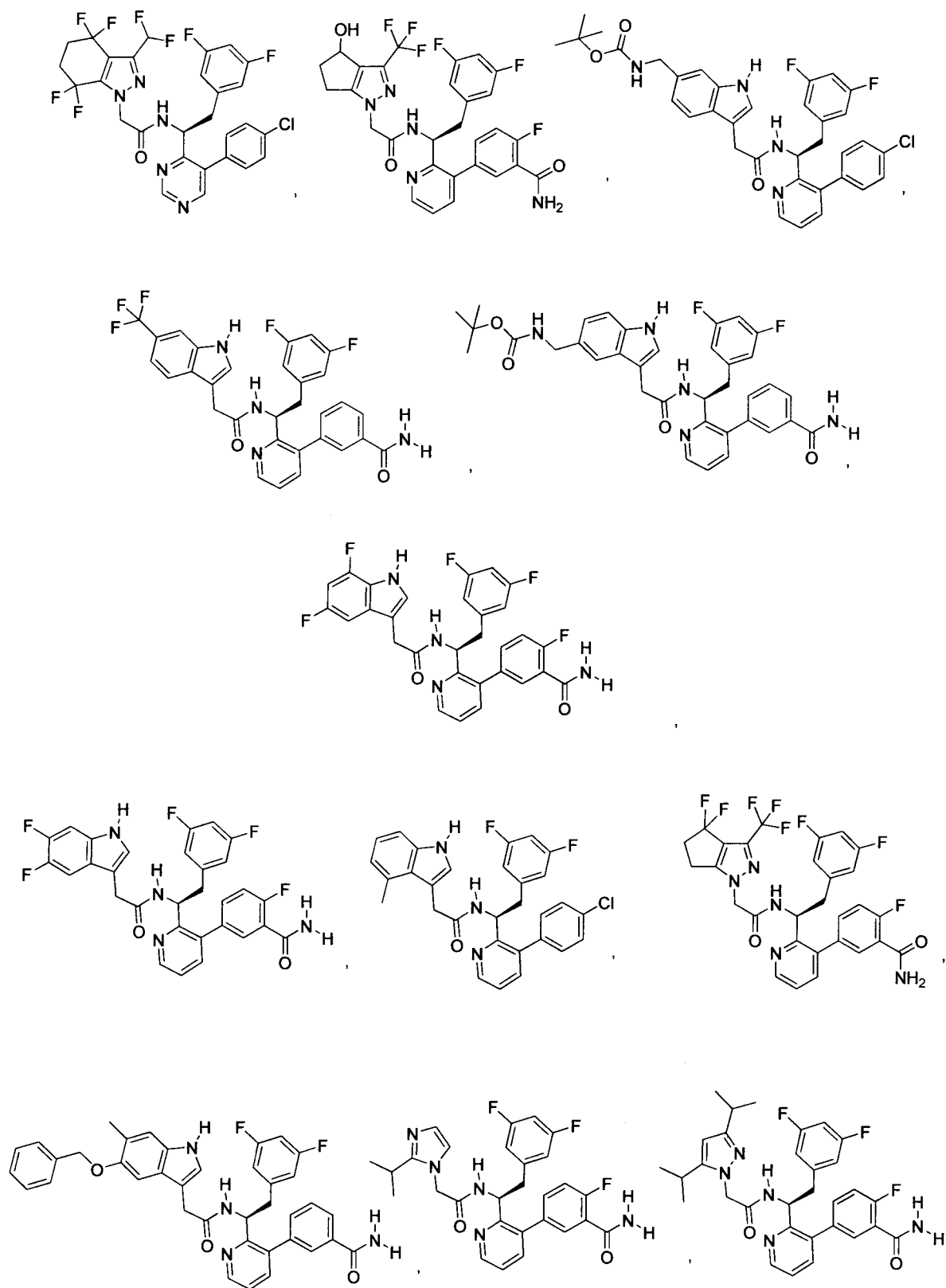


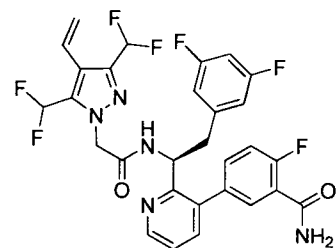
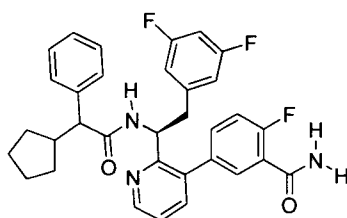
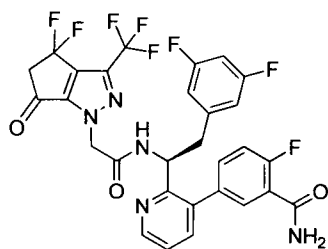
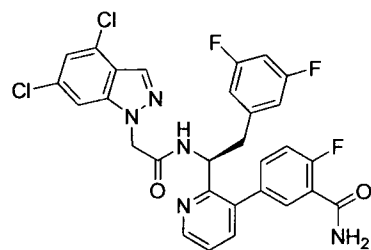
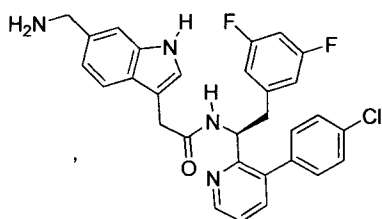
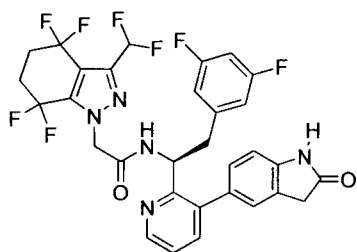
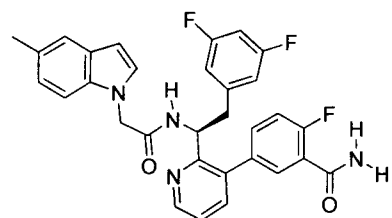
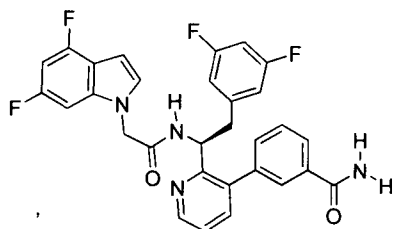
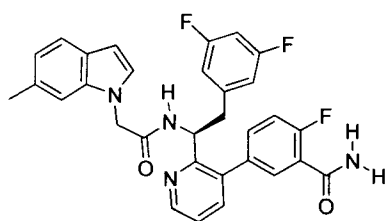
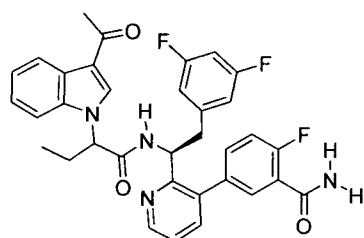
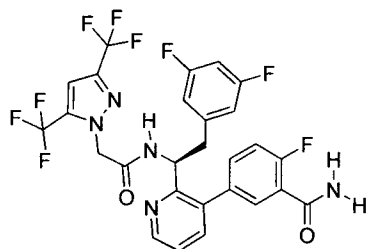
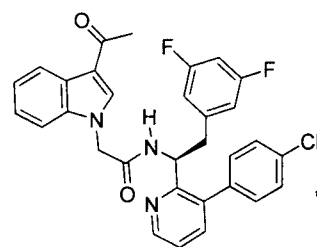
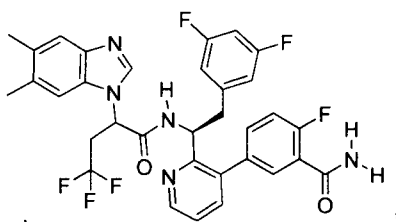
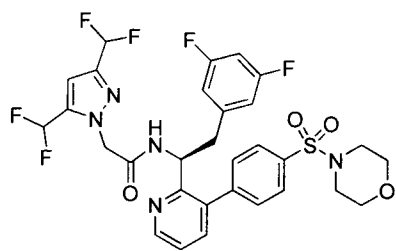


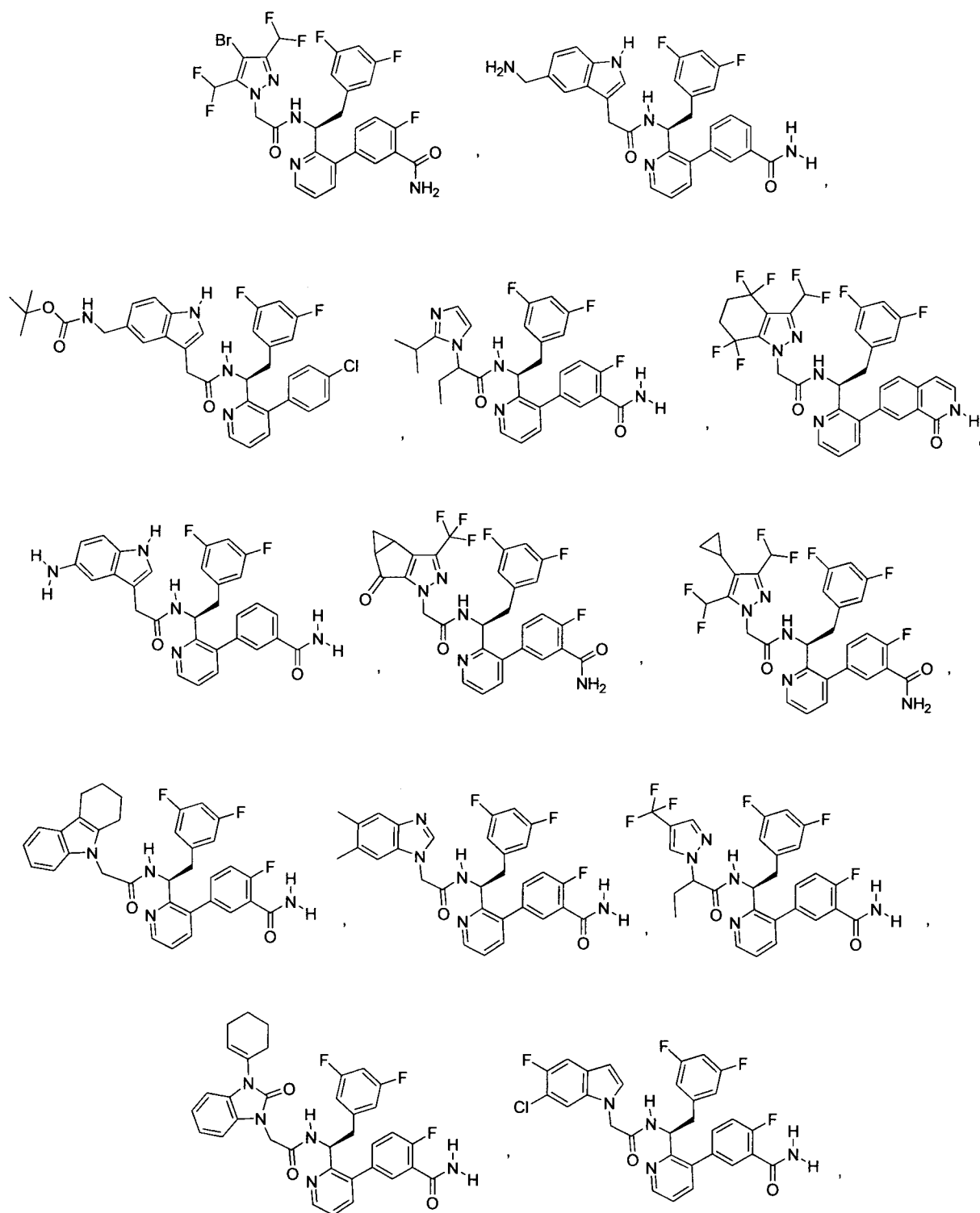


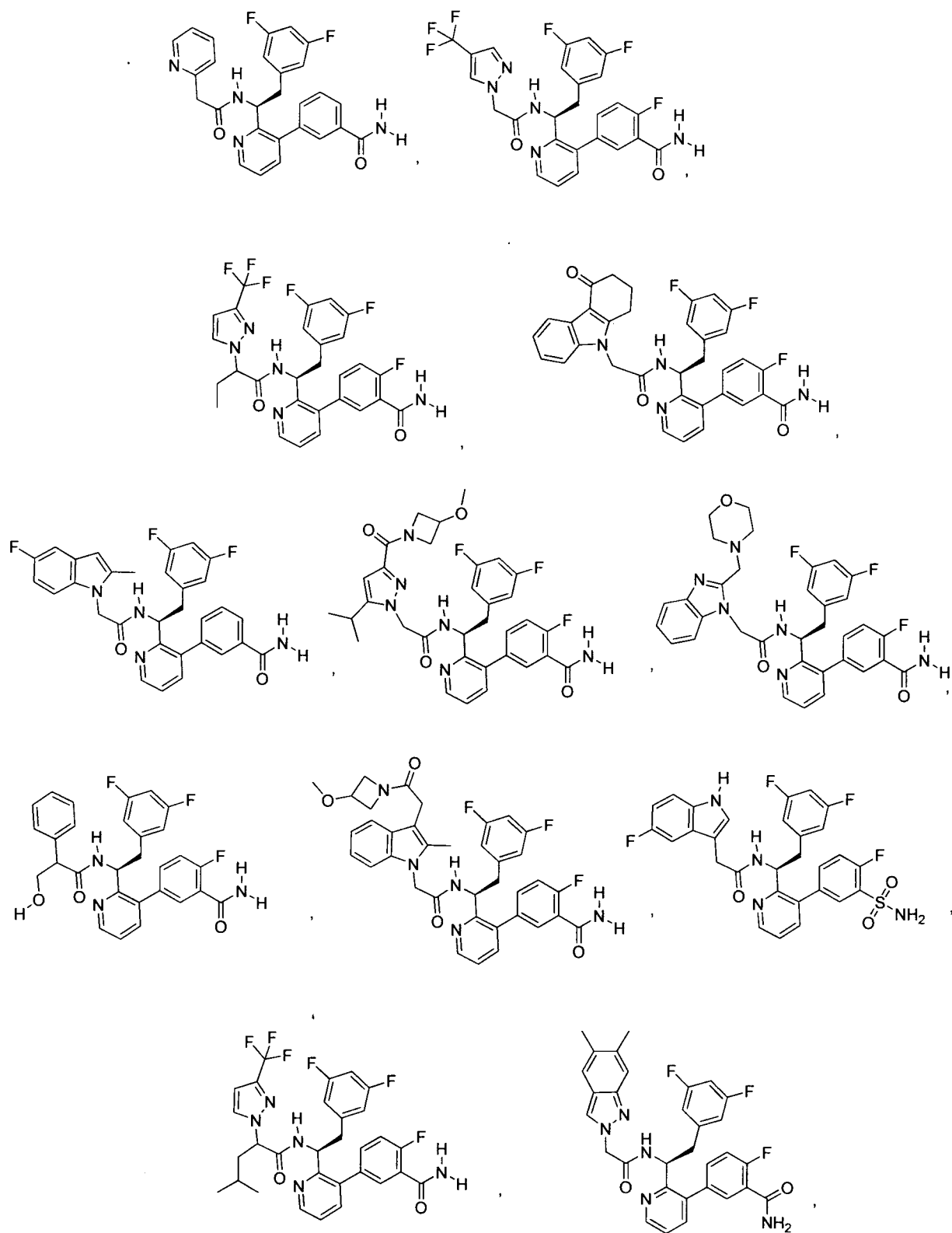


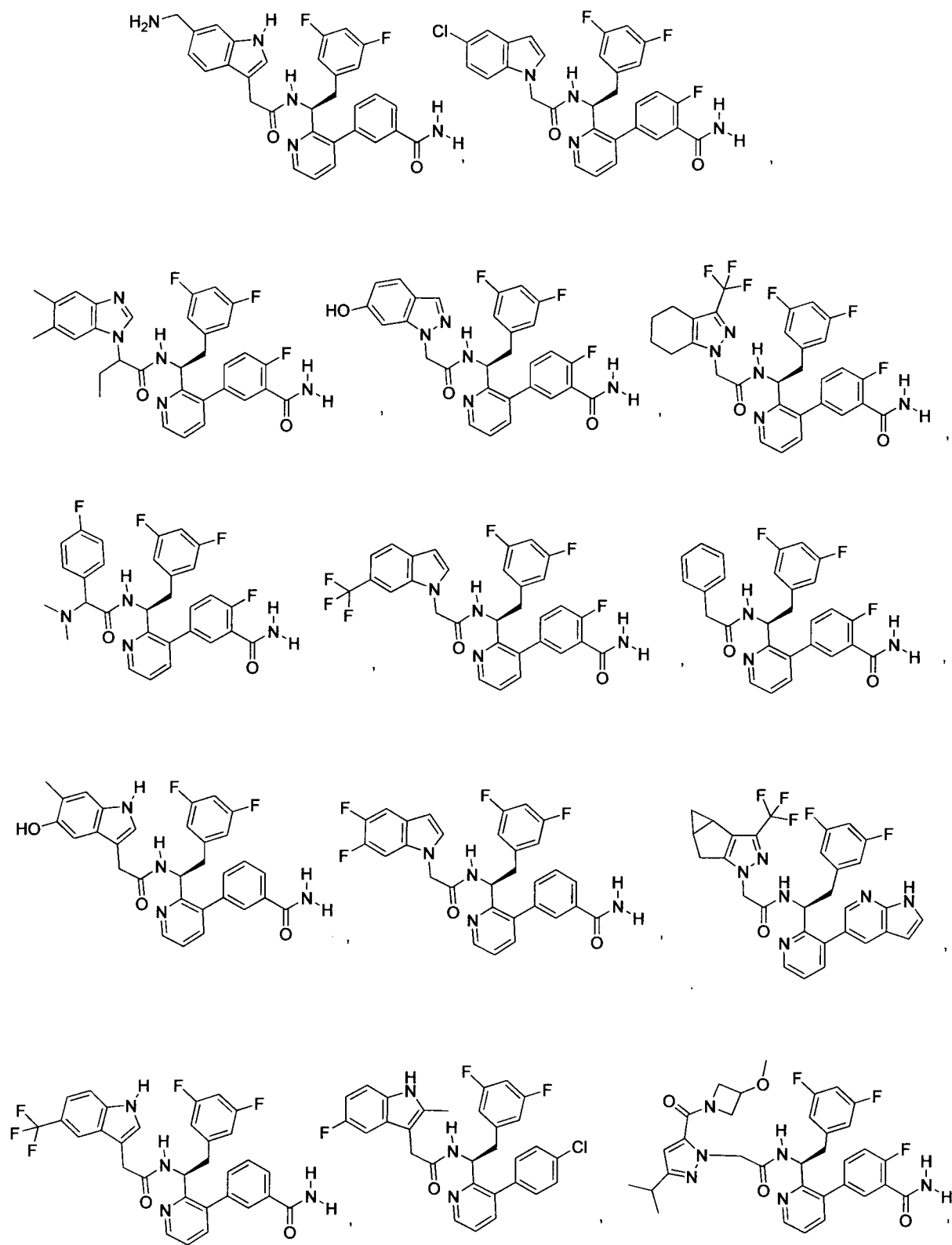


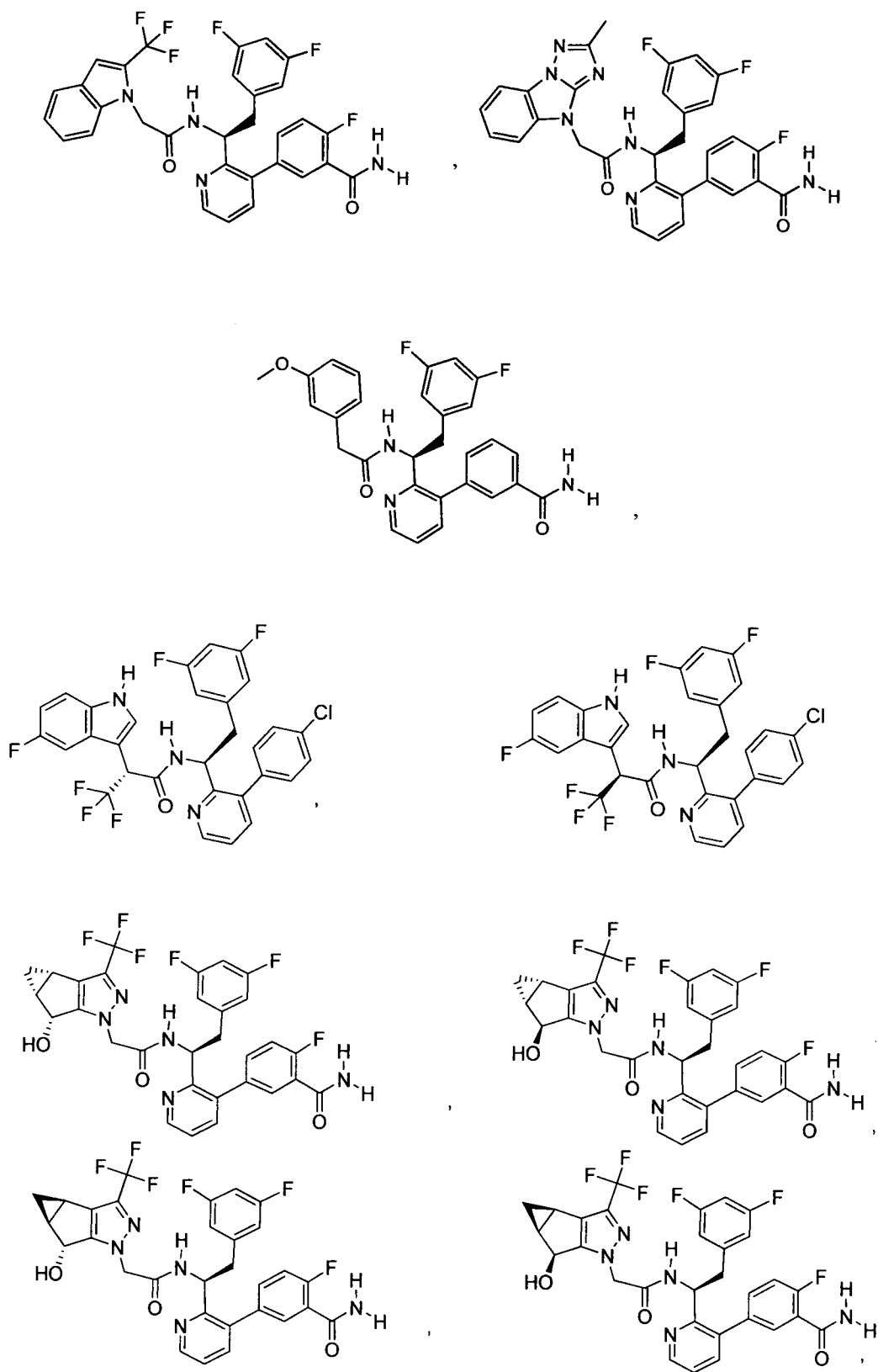


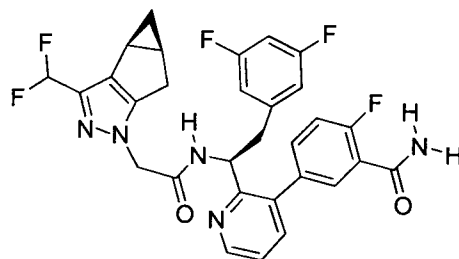
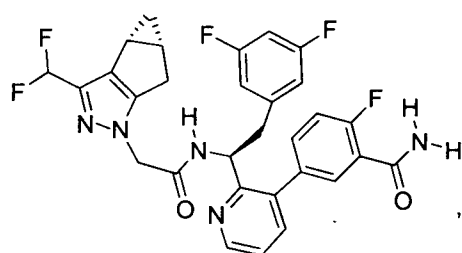
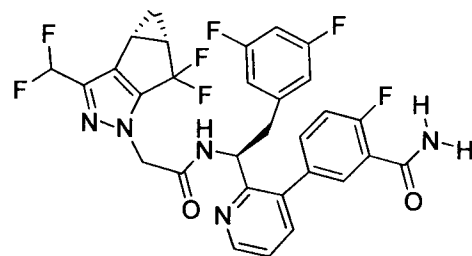
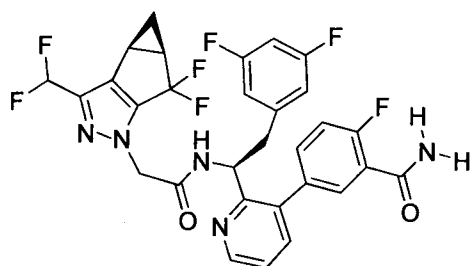
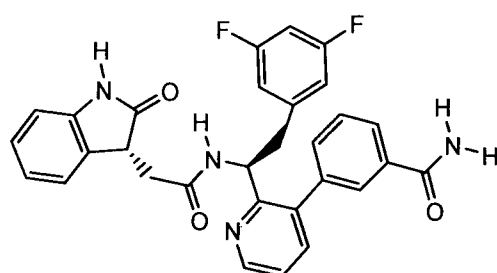
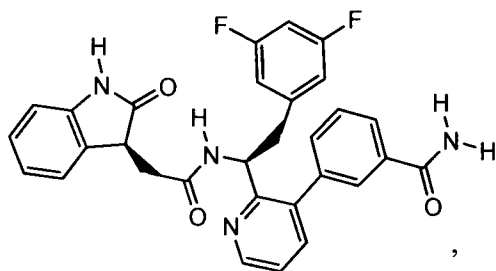
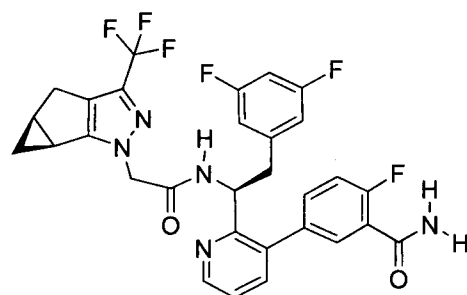
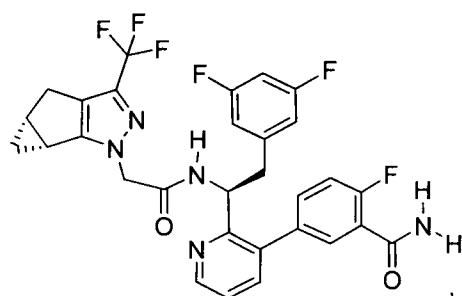
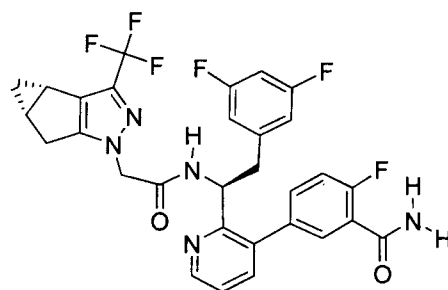
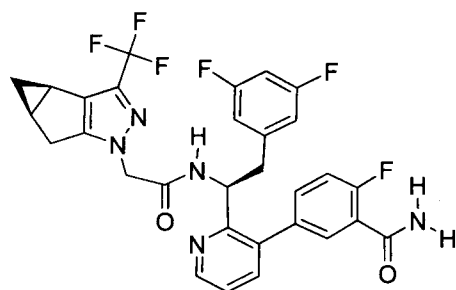


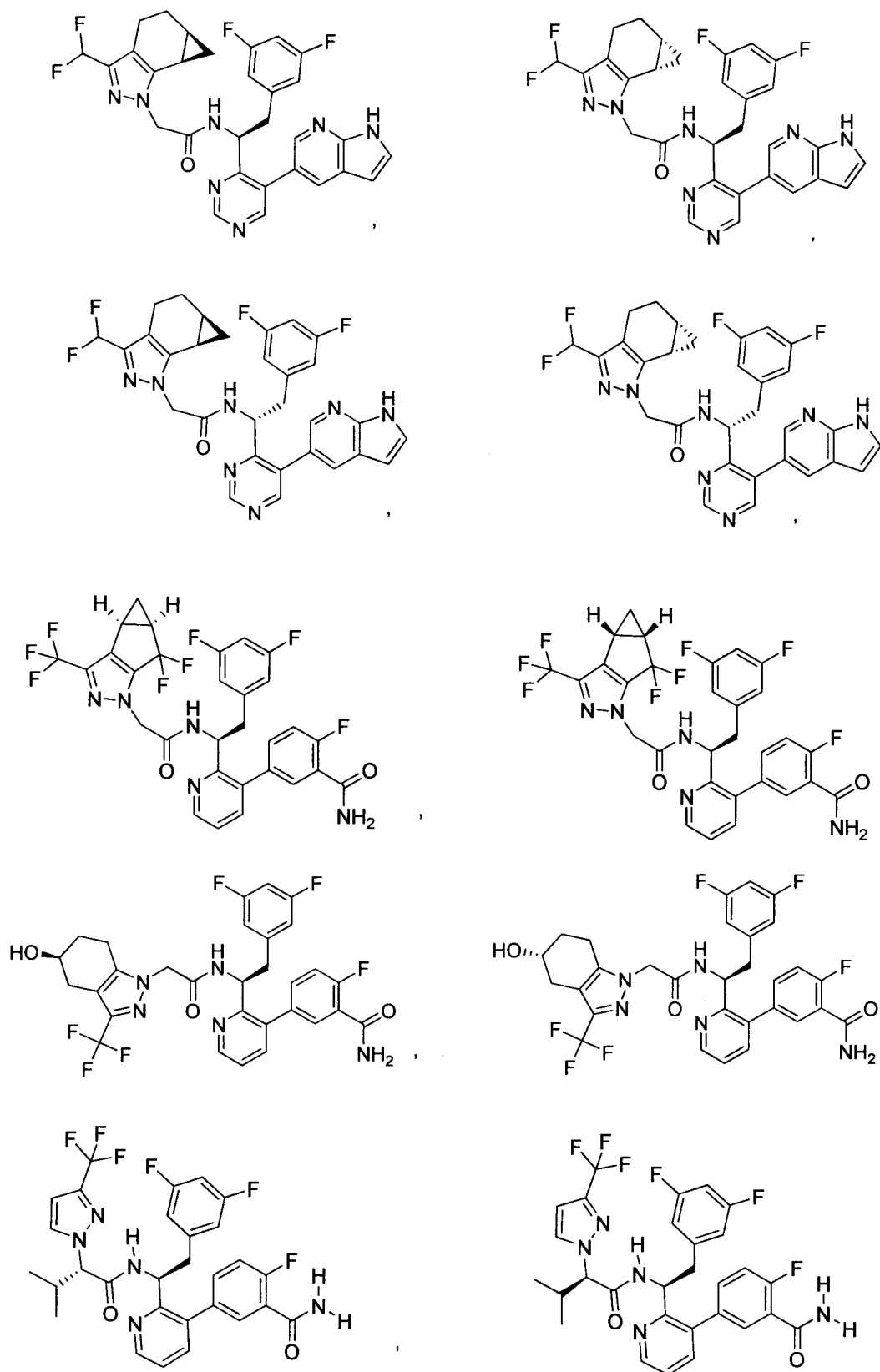


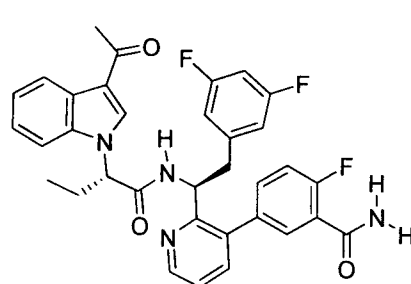
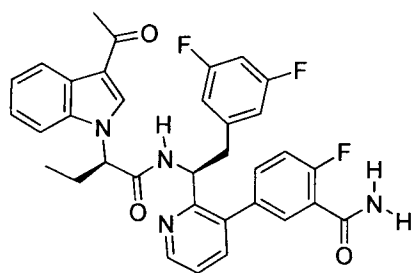
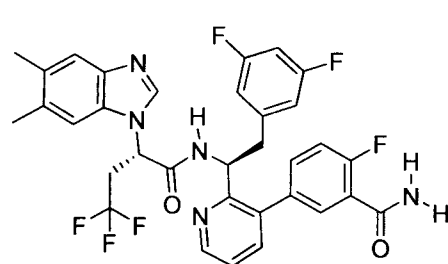
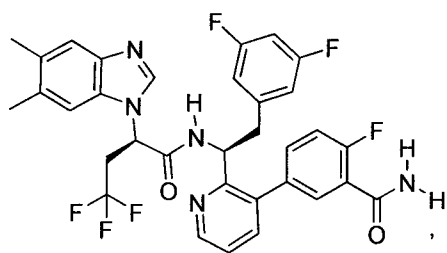
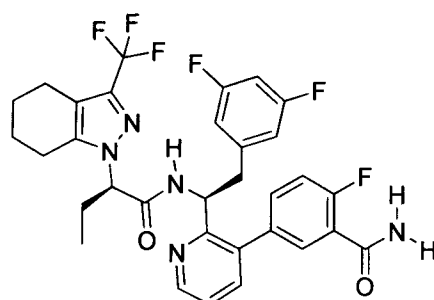
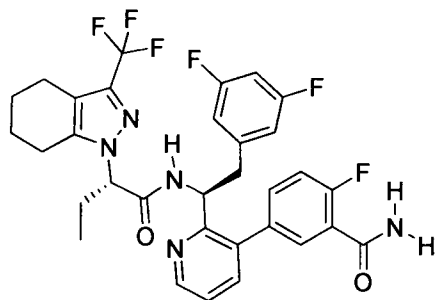
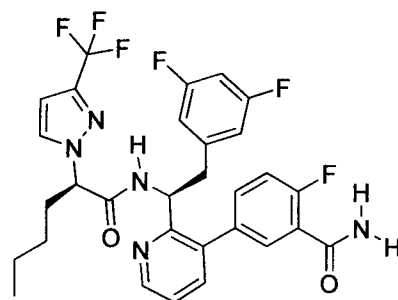
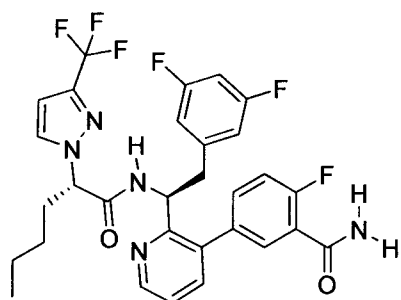
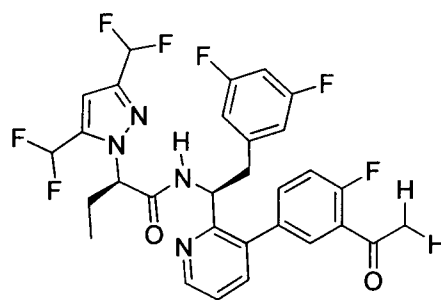
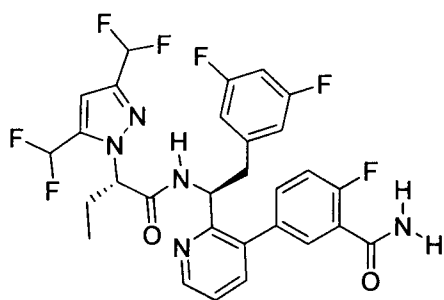


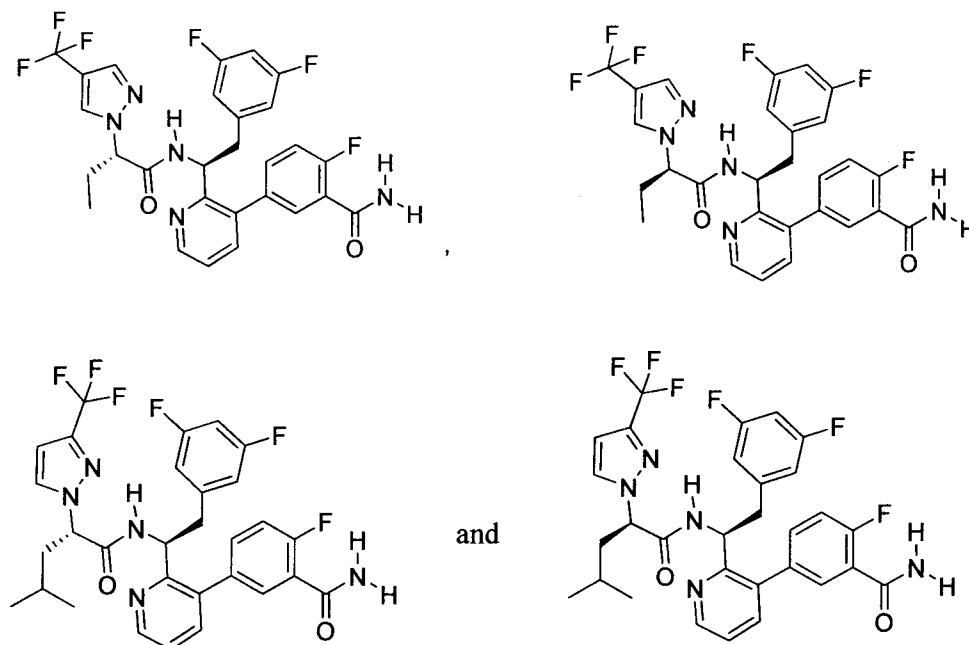






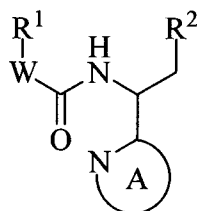






and salts thereof.

41. The compound of claim 1 which is a compound of formula I':



I'

wherein:

A is a 6-membered heteroaryl comprising one or two nitrogens, wherein the 6-membered heteroaryl is substituted with one Z¹ group and optionally substituted with one or more Z² groups;

W is CR^{3a}R^{3b}, O or NR⁴;

R¹ is aryl, heteroaryl or heterocycle, wherein any aryl, heteroaryl or heterocycle of R¹ is optionally substituted with one or more Z³ groups;

R² is a 6-membered aryl, 5-membered heteroaryl or 6-membered heteroaryl, wherein any 6-membered aryl, 5-membered heteroaryl or 6-membered heteroaryl of R² is optionally substituted with one or more Z⁴ groups;

each R^{3a} and R^{3b} is independently selected from H, halogen, (C₁-C₃)alkyl, (C₁-C₃)haloalkyl, (C₁-C₆)heteroalkyl, heteroaryl(C₁-C₆)alkyl-, heterocyclyl(C₁-C₆)alkyl-,

$-\text{NR}_a\text{R}_b$, and $-\text{NR}_c\text{COR}_d$; or R^{3a} and R^{3b} together with the carbon to which they are attached form a (C₃-C₆)carbocycle;

R^4 is selected from H, (C₁-C₆)alkyl, (C₃-C₆)carbocycle, aryl(C₁-C₆)alkyl and heteroaryl(C₁-C₆)alkyl-;

R_a and R_b are each independently selected from H, (C₁-C₈)alkyl, (C₂-C₈)alkenyl, (C₂-C₈)alkynyl, (C₃-C₇)carbocycle, heterocycle, heteroaryl, aryl, haloaryl, haloheteroaryl, haloheterocycle, (C₁-C₈)haloalkyl and (C₁-C₈)heteroalkyl, or R_a and R_b together with the nitrogen to which they are attached form a 5, 6 or 7-membered heterocycle;

each R_c is independently selected from H, (C₁-C₈)alkyl, (C₂-C₈)alkenyl, (C₂-C₈)alkynyl, (C₃-C₇)carbocycle, heterocycle, heteroaryl, aryl, haloaryl, haloheteroaryl, haloheterocycle, (C₁-C₈)haloalkyl and (C₁-C₈)heteroalkyl;

each R_d is independently selected from (C₁-C₈)alkyl, (C₂-C₈)alkenyl, (C₂-C₈)alkynyl, (C₃-C₇)carbocycle, heterocycle, heteroaryl, aryl, haloaryl, haloheteroaryl, haloheterocycle, (C₁-C₈)haloalkyl and (C₁-C₈)heteroalkyl;

each Z^1 is independently selected from (C₂-C₈)alkenyl, (C₂-C₈)alkynyl, (C₃-C₇)carbocycle, aryl, heteroaryl, heterocycle and $-\text{OR}_{n1}$, wherein any (C₃-C₇)carbocycle, aryl, heteroaryl and heterocycle of Z^1 is optionally substituted with one or more Z^{1a} or Z^{1b} groups and wherein any (C₁-C₈)alkyl, (C₂-C₈)alkenyl and (C₂-C₈)alkynyl of Z^1 is optionally substituted with one or more Z^{1a} groups;

each Z^{1a} is independently selected from (C₃-C₇)carbocycle, aryl, heteroaryl, heterocycle, halogen, $-\text{CN}$, $-\text{OR}_{n2}$, $-\text{OC}(\text{O})\text{R}_{p2}$, $-\text{OC}(\text{O})\text{NR}_{q2}\text{R}_{r2}$, $-\text{SR}_{n2}$, $-\text{S}(\text{O})\text{R}_{p2}$, $-\text{S}(\text{O})_2\text{OH}$, $-\text{S}(\text{O})_2\text{R}_{p2}$, $-\text{S}(\text{O})_2\text{NR}_{q2}\text{R}_{r2}$, $-\text{NR}_{q2}\text{R}_{r2}$, $-\text{NR}_{n2}\text{COR}_{p2}$, $-\text{NR}_{n2}\text{CO}_2\text{R}_{p2}$, $-\text{NR}_{n2}\text{CONR}_{q2}\text{R}_{r2}$, $-\text{NR}_{n2}\text{S}(\text{O})_2\text{R}_{p2}$, $-\text{NR}_{n2}\text{S}(\text{O})_2\text{OR}_{p2}$, $-\text{NR}_{n2}\text{S}(\text{O})_2\text{NR}_{q2}\text{R}_{r2}$, NO_2 , $-\text{C}(\text{O})\text{R}_{n2}$, $-\text{C}(\text{O})\text{OR}_{n2}$, and, $-\text{C}(\text{O})\text{NR}_{q2}\text{R}_{r2}$, wherein any (C₃-C₇)carbocycle, aryl, heteroaryl and heterocycle of Z^{1a} is optionally substituted with one or more Z^{1c} or Z^{1d} groups;

each Z^{1b} is independently selected from (C₁-C₈)alkyl, (C₂-C₈)alkenyl and (C₂-C₈)alkynyl, wherein any (C₁-C₈)alkyl, (C₂-C₈)alkenyl and (C₂-C₈)alkynyl of Z^{1b} is optionally substituted with one or more Z^{1c} groups;

each Z^{1c} is independently selected from (C₃-C₇)carbocycle, aryl, heteroaryl, heterocycle, halogen, $-\text{CN}$, $-\text{OR}_{n3}$, $-\text{OC}(\text{O})\text{R}_{p3}$, $-\text{OC}(\text{O})\text{NR}_{q3}\text{R}_{r3}$, $-\text{SR}_{n3}$, $-\text{S}(\text{O})\text{R}_{p3}$, $-\text{S}(\text{O})_2\text{OH}$, $-\text{S}(\text{O})_2\text{R}_{p3}$, $-\text{S}(\text{O})_2\text{NR}_{q3}\text{R}_{r3}$, $-\text{NR}_{q3}\text{R}_{r3}$, $-\text{NR}_{n3}\text{COR}_{p3}$, $-\text{NR}_{n3}\text{CO}_2\text{R}_{p3}$, $-\text{NR}_{n3}\text{CONR}_{q3}\text{R}_{r3}$, $-\text{NR}_{n3}\text{S}(\text{O})_2\text{R}_{p3}$, $-\text{NR}_{n3}\text{S}(\text{O})_2\text{OR}_{p3}$, $-\text{NR}_{n3}\text{S}(\text{O})_2\text{NR}_{q3}\text{R}_{r3}$, NO_2 , $-\text{C}(\text{O})\text{R}_{n3}$, $-\text{C}(\text{O})\text{OR}_{n3}$, $-\text{C}(\text{O})\text{NR}_{q3}\text{R}_{r3}$, haloaryl, haloheteroaryl, haloheterocycle and (C₁-C₈)heteroalkyl;

each Z^{1d} is independently selected from (C₁-C₈)alkyl, (C₂-C₈)alkenyl, (C₂-C₈)alkynyl and (C₁-C₈)haloalkyl;

each R_{n1} is independently selected from (C₁-C₈)alkyl, (C₂-C₈)alkenyl, (C₂-C₈)alkynyl, (C₃-C₇)carbocycle, heterocycle, heteroaryl and aryl, wherein any (C₃-C₇)carbocycle, aryl, heteroaryl and heterocycle of R_{n1} is optionally substituted with one or more Z^{1a} or Z^{1b} groups, and wherein any (C₁-C₈)alkyl, (C₂-C₈)alkenyl and (C₂-C₈)alkynyl of R_{n1} is optionally substituted with one or more Z^{1a} groups;

each R_{n2} is independently selected from H, (C₁-C₈)alkyl, (C₂-C₈)alkenyl, (C₂-C₈)alkynyl, (C₃-C₇)carbocycle, heterocycle, heteroaryl and aryl, wherein any (C₃-C₇)carbocycle, aryl, heteroaryl and heterocycle of R_{n2} is optionally substituted with one or more Z^{1c} or Z^{1d} groups, and wherein any (C₁-C₈)alkyl, (C₂-C₈)alkenyl and (C₂-C₈)alkynyl of R_{n2} is optionally substituted with one or more Z^{1c} groups;

each R_{p2} is independently selected from (C₁-C₈)alkyl, (C₂-C₈)alkenyl, (C₂-C₈)alkynyl, (C₃-C₇)carbocycle, heterocycle, heteroaryl and aryl, wherein any (C₃-C₇)carbocycle, aryl, heteroaryl and heterocycle of R_{p2} is optionally substituted with one or more Z^{1c} or Z^{1d} groups, and wherein any (C₁-C₈)alkyl, (C₂-C₈)alkenyl and (C₂-C₈)alkynyl of R_{p2} is optionally substituted with one or more Z^{1c} groups;

R_{q2} and R_{r2} are each independently selected from H, (C₁-C₈)alkyl, (C₂-C₈)alkenyl, (C₂-C₈)alkynyl, (C₃-C₇)carbocycle, heterocycle, heteroaryl and aryl, wherein any (C₃-C₇)carbocycle, aryl, heteroaryl and heterocycle of R_{q2} or R_{r2} is optionally substituted with one or more Z^{1c} or Z^{1d} groups, and wherein any (C₁-C₈)alkyl, (C₂-C₈)alkenyl and (C₂-C₈)alkynyl of R_{q2} or R_{r2} is optionally substituted with one or more Z^{1c} groups, or R_{q2} and R_{r2} 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 Z^{1c} or Z^{1d} groups;

each R_{n3} is independently selected from H, (C₁-C₈)alkyl, (C₂-C₈)alkenyl, (C₂-C₈)alkynyl, (C₃-C₇)carbocycle, heterocycle, heteroaryl, aryl, haloaryl, haloheteroaryl, haloheterocycle, (C₁-C₈)haloalkyl and (C₁-C₈)heteroalkyl;

each R_{p3} is independently selected from (C₁-C₈)alkyl, (C₂-C₈)alkenyl, (C₂-C₈)alkynyl, (C₃-C₇)carbocycle, heterocycle, heteroaryl, aryl, haloaryl, haloheteroaryl, haloheterocycle, (C₁-C₈)haloalkyl and (C₁-C₈)heteroalkyl;

R_{q3} and R_{r3} are each independently selected from H, (C₁-C₈)alkyl, (C₂-C₈)alkenyl, (C₂-C₈)alkynyl, (C₃-C₇)carbocycle, heterocycle, heteroaryl, aryl, haloaryl, haloheteroaryl, haloheterocycle, (C₁-C₈)haloalkyl and (C₁-C₈)heteroalkyl, or R_{q3} and R_{r3} together with the nitrogen to which they are attached form a 5, 6 or 7-membered heterocycle;

each Z^2 is independently selected from (C₁-C₆)alkyl, (C₁-C₆)haloalkyl, (C₃-C₇)carbocycle, halogen, CN, OH and -O(C₁-C₆)alkyl;

each Z^3 is independently selected from (C₁-C₈)alkyl, (C₂-C₈)alkenyl, (C₂-C₈)alkynyl, (C₃-C₇)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)₂OH, -S(O)₂R_{p4}, -S(O)₂NR_{q4}R_{r4}, -NR_{q4}R_{r4}, -NR_{n4}COR_{p4}, -NR_{n4}CO₂R_{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}, NO₂, -C(O)R_{n4}, -C(O)OR_{n4}, and -C(O)NR_{q4}R_{r4}, wherein any (C₃-C₇)carbocycle, aryl, heteroaryl and heterocycle of Z^3 is optionally substituted with one or more Z^{3a} or Z^{3b} groups, and wherein any (C₁-C₈)alkyl, (C₂-C₈)alkenyl and (C₂-C₈)alkynyl of Z^3 is optionally substituted with one or more Z^{3a} groups;

each Z^{3a} is independently selected from (C₃-C₇)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)₂OH, -S(O)₂R_{p5}, -S(O)₂NR_{q5}R_{r5}, -NR_{q5}R_{r5}, -NR_{n5}COR_{p5}, -NR_{n5}CO₂R_{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}, NO₂, -C(O)R_{n5}, -C(O)OR_{n5}, and -C(O)NR_{q5}R_{r5}, wherein any (C₃-C₇)carbocycle, aryl, heteroaryl and heterocycle of Z^{3a} is optionally substituted with one or more Z^{3c} or Z^{3d} groups;

each Z^{3b} is independently selected from (C₁-C₈)alkyl, (C₂-C₈)alkenyl and (C₂-C₈)alkynyl, wherein any (C₁-C₈)alkyl, (C₂-C₈)alkenyl and (C₂-C₈)alkynyl of Z^{3b} is optionally substituted with one or more Z^{3c} groups;

each Z^{3c} is independently selected from (C₃-C₇)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)₂OH, -S(O)₂R_{p6}, -S(O)₂NR_{q6}R_{r6}, -NR_{q6}R_{r6}, -NR_{n6}COR_{p6}, -NR_{n6}CO₂R_{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}, NO₂, -C(O)R_{n6}, -C(O)OR_{n6}, -C(O)NR_{q6}R_{r6}, haloaryl, haloheteroaryl, haloheterocycle and (C₁-C₈)heteroalkyl;

each Z^{3d} is independently selected from (C₁-C₈)alkyl, (C₂-C₈)alkenyl, (C₂-C₈)alkynyl, and (C₁-C₈)haloalkyl;

each R_{n4} is independently selected from H, (C₁-C₈)alkyl, (C₂-C₈)alkenyl, (C₂-C₈)alkynyl, (C₃-C₇)carbocycle, heterocycle, heteroaryl and aryl, wherein any (C₃-C₇)carbocycle, aryl, heteroaryl and heterocycle of R_{n4} is optionally substituted with one or more Z^{3a} or Z^{3b} groups, and wherein any (C₁-C₈)alkyl, (C₂-C₈)alkenyl and (C₂-C₈)alkynyl of R_{n4} is optionally substituted with one or more Z^{3a} groups;

each R_{p4} is independently selected from (C₁-C₈)alkyl, (C₂-C₈)alkenyl, (C₂-C₈)alkynyl, (C₃-C₇)carbocycle, heterocycle, heteroaryl and aryl, wherein any (C₃-C₇)carbocycle, aryl, heteroaryl, or heterocycle of R_{p4} is optionally substituted with one or more Z^{3a} or Z^{3b} groups, and wherein any (C₁-C₈)alkyl, (C₂-C₈)alkenyl or (C₂-C₈)alkynyl of R_{p4} is optionally substituted with one or more Z^{3a} groups;

R_{q4} and R_{r4} are each independently selected from H, (C₁-C₈)alkyl, (C₂-C₈)alkenyl, (C₂-C₈)alkynyl, (C₃-C₇)carbocycle, heterocycle, heteroaryl and aryl, wherein any (C₃-C₇)carbocycle, aryl, heteroaryl and heterocycle of R_{q4} or R_{r4} is optionally substituted with one or more Z^{3a} or Z^{3b} groups, and wherein any (C₁-C₈)alkyl, (C₂-C₈)alkenyl and (C₂-C₈)alkynyl of R_{q4} or R_{r4} is optionally substituted with one or more Z^{3a} groups, or R_{q4} and R_{r4} 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 Z^{3a} or Z^{3b} groups;

each R_{n5} is independently selected from H, (C₁-C₈)alkyl, (C₂-C₈)alkenyl, (C₂-C₈)alkynyl, (C₃-C₇)carbocycle, heterocycle, heteroaryl and aryl, wherein any (C₃-C₇)carbocycle, aryl, heteroaryl and heterocycle of R_{n5} is optionally substituted with one or more Z^{3c} or Z^{3d} groups, and wherein any (C₁-C₈)alkyl, (C₂-C₈)alkenyl and (C₂-C₈)alkynyl of R_{n5} is optionally substituted with one or more Z^{3c} groups;

each R_{p5} is independently selected from (C₁-C₈)alkyl, (C₂-C₈)alkenyl, (C₂-C₈)alkynyl, (C₃-C₇)carbocycle, heterocycle, heteroaryl and aryl, wherein any (C₃-C₇)carbocycle, aryl, heteroaryl and heterocycle of R_{p5} is optionally substituted with one or more Z^{3c} or Z^{3d} groups, and wherein any (C₁-C₈)alkyl, (C₂-C₈)alkenyl and (C₂-C₈)alkynyl of R_{p5} is optionally substituted with one or more Z^{3c} groups;

R_{q5} and R_{r5} are each independently selected from H, (C₁-C₈)alkyl, (C₂-C₈)alkenyl, (C₂-C₈)alkynyl, (C₃-C₇)carbocycle, heterocycle, heteroaryl and aryl, wherein any (C₃-C₇)carbocycle, aryl, heteroaryl and heterocycle of R_{q5} or R_{r5} is optionally substituted with one or more Z^{3c} or Z^{3d} groups, and wherein any (C₁-C₈)alkyl, (C₂-C₈)alkenyl and (C₂-C₈)alkynyl of R_{q5} or R_{r5} is optionally substituted with one or more Z^{3c} 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 Z^{3c} or Z^{3d} groups;

each R_{n6} is independently selected from H, (C₁-C₈)alkyl, (C₂-C₈)alkenyl, (C₂-C₈)alkynyl, (C₃-C₇)carbocycle, heterocycle, heteroaryl, aryl, haloaryl, haloheteroaryl, haloheterocycle, (C₁-C₈)haloalkyl and (C₁-C₈)heteroalkyl;

each R_{p6} is independently selected from (C₁-C₈)alkyl, (C₂-C₈)alkenyl, (C₂-C₈)alkynyl, (C₃-C₇)carbocycle, heterocycle, heteroaryl, aryl, haloaryl, haloheteroaryl, haloheterocycle, (C₁-C₈)haloalkyl and (C₁-C₈)heteroalkyl;

R_{q6} and R_{r6} are each independently selected from H, (C₁-C₈)alkyl, (C₂-C₈)alkenyl, (C₂-C₈)alkynyl, (C₃-C₇)carbocycle, heterocycle, heteroaryl, aryl, haloaryl, haloheteroaryl, haloheterocycle, (C₁-C₈)haloalkyl and (C₁-C₈)heteroalkyl, or R_{q6} and R_{r6} together with the nitrogen to which they are attached form a 5, 6 or 7-membered heterocycle;

each Z^4 is independently selected from (C₁-C₈)alkyl, (C₂-C₈)alkenyl, (C₂-C₈)alkynyl, (C₃-C₇)carbocycle, aryl, heteroaryl, heterocycle, halogen, -CN, -OR_{n8}, -OC(O)R_{p8}, -OC(O)NR_{q8}R_{r8}, -SR_{n8}, -S(O)R_{p8}, -S(O)₂OH, -S(O)₂R_{p8}, -S(O)₂NR_{q8}R_{r8}, -NR_{q8}R_{r8}, -NR_{n8}COR_{p8}, -NR_{n8}CO₂R_{p8}, -NR_{n8}CONR_{q8}R_{r8}, -NR_{n8}S(O)₂R_{p8}, -NR_{n8}S(O)₂OR_{p8}, -NR_{n8}S(O)₂NR_{q8}R_{r8}, NO₂, -C(O)R_{n8}, -C(O)OR_{n8}, and -C(O)NR_{q8}R_{r8}, wherein any (C₃-C₇)carbocycle, aryl, heteroaryl and heterocycle of Z^4 is optionally substituted with one or more Z^{4c} or Z^{4d} groups and wherein any (C₁-C₈)alkyl, (C₂-C₈)alkenyl and (C₂-C₈)alkynyl of Z^4 is optionally substituted with one or more Z^{4c} groups;

each Z^{4c} is independently selected from of (C₃-C₇)carbocycle, aryl, heteroaryl, heterocycle, halogen, -CN, -OR_{n9}, -OC(O)R_{p9}, -OC(O)NR_{q9}R_{r9}, -SR_{n9}, -S(O)R_{p9}, -S(O)₂OH, -S(O)₂R_{p9}, -S(O)₂NR_{q9}R_{r9}, -NR_{q9}R_{r9}, -NR_{n9}COR_{p9}, -NR_{n9}CO₂R_{p9}, -NR_{n9}CONR_{q9}R_{r9}, -NR_{n9}S(O)₂R_{p9}, -NR_{n9}S(O)₂OR_{p9}, -NR_{n9}S(O)₂NR_{q9}R_{r9}, NO₂, -C(O)R_{n9}, -C(O)OR_{n9}, -C(O)NR_{q9}R_{r9}, haloaryl, haloheteroaryl, haloheterocycle and (C₁-C₈)heteroalkyl;

each Z^{4d} is independently selected from of (C₁-C₈)alkyl, (C₂-C₈)alkenyl, (C₂-C₈)alkynyl and (C₁-C₈)haloalkyl;

each R_{n8} is independently selected from H, (C₁-C₈)alkyl, (C₂-C₈)alkenyl, (C₂-C₈)alkynyl, (C₃-C₇)carbocycle, heterocycle, heteroaryl and aryl, wherein any (C₃-C₇)carbocycle, aryl, heteroaryl and heterocycle of R_{n8} is optionally substituted with one or more Z^{4c} or Z^{4d} groups, and wherein any (C₁-C₈)alkyl, (C₂-C₈)alkenyl or (C₂-C₈)alkynyl of R_{n8} is optionally substituted with one or more Z^{4c} groups;

each R_{p8} is independently selected from (C₁-C₈)alkyl, (C₁-C₆)haloalkyl, (C₂-C₈)alkenyl, (C₂-C₈)alkynyl, (C₃-C₇)carbocycle, heterocycle, heteroaryl and aryl, wherein any (C₃-C₇)carbocycle, aryl, heteroaryl and heterocycle of R_{p8} is optionally substituted with one or more Z^{4c} or Z^{4d} groups, and wherein any (C₁-C₈)alkyl, (C₂-C₈)alkenyl and (C₂-C₈)alkynyl of R_{p8} is optionally substituted with one or more Z^{4c} groups;

R_{q8} and R_{r8} are each independently selected from H, (C₁-C₈)alkyl, (C₂-C₈)alkenyl, (C₂-C₈)alkynyl, (C₃-C₇)carbocycle, heterocycle, heteroaryl and aryl, wherein any (C₃-C₇)carbocycle, aryl, heteroaryl and heterocycle of R_{q8} or R_{r8} is optionally substituted with one or more Z^{4c} or Z^{4d} groups, and wherein any (C₁-C₈)alkyl, (C₂-C₈)alkenyl and (C₂-C₈)alkynyl of R_{q8} or R_{r8} is optionally substituted with one or more Z^{4c} groups, or R_{q8} and R_{r8} 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 Z^{4c} or Z^{4d} groups;

each R_{n9} is independently selected from H, (C₁-C₈)alkyl, (C₂-C₈)alkenyl, (C₂-C₈)alkynyl, (C₃-C₇)carbocycle, heterocycle, heteroaryl, aryl, haloaryl, haloheteroaryl, haloheterocycle, (C₁-C₈)haloalkyl and (C₁-C₈)heteroalkyl;

each R_{p9} is independently selected from (C₁-C₈)alkyl, (C₂-C₈)alkenyl, (C₂-C₈)alkynyl, (C₃-C₇)carbocycle, heterocycle, heteroaryl, aryl, haloaryl, haloheteroaryl, haloheterocycle, (C₁-C₈)haloalkyl and (C₁-C₈)heteroalkyl; and

R_{q9} and R_{r9} are each independently selected from H, (C₁-C₈)alkyl, (C₂-C₈)alkenyl, (C₂-C₈)alkynyl, (C₃-C₇)carbocycle, heterocycle, heteroaryl, aryl, haloaryl, haloheteroaryl, haloheterocycle, (C₁-C₈)haloalkyl and (C₁-C₈)heteroalkyl; or R_{q9} and R_{r9} together with the nitrogen to which they are attached form a 5, 6 or 7-membered heterocycle;

or a salt thereof.

42. A pharmaceutical composition comprising a compound of formula I as described in any one of claims 1-41, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier.

43. A method for treating a *Retroviridae* virus infection in a mammal comprising administering a therapeutically effective amount of a compound of any one of claims 1-41, or a pharmaceutically acceptable salt thereof, to the mammal.

44. The method of claim 43 wherein the viral infection is caused by an HIV virus.

45. A method for treating an HIV infection in a mammal comprising administering a compound of formula I as described in any one of claims 1-41, or a pharmaceutically acceptable salt thereof, to the mammal.

46. 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 formula I as described in any one of claims 1-41, 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 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.

47. A compound of formula I as described in any of claims 1-4, or a pharmaceutically acceptable salt thereof for use in medical therapy.

48. A compound of formula I as described in any one of claims 1-41 or a pharmaceutically acceptable salt thereof, for the prophylactic or therapeutic treatment of a *Retroviridae* virus infection or an HIV virus infection.

49. The use of a compound as described in any one of claims 1-41 or a pharmaceutically acceptable salt thereof, for the manufacture of a medicament for treating a *Retroviridae* virus infection or an HIV virus infection in a mammal.

INTERNATIONAL SEARCH REPORT

International application No
PCT/US2012/045630

A. CLASSIFICATION OF SUBJECT MATTER INV. C07D213/40 C07D401/12 C07D401/14 C07D403/12 C07D403/14 C07D405/12 C07D471/04 C07D471/06 C07D487/04 C07D491/04 C07D495/04 A61K31/496 A61P31/14											
According to International Patent Classification (IPC) or to both national classification and IPC											
B. FIELDS SEARCHED Minimum documentation searched (classification system followed by classification symbols) C07D A61K A61P Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched Electronic data base consulted during the international search (name of data base and, where practicable, search terms used) EPO-Internal, CHEM ABS Data, WPI Data											
C. DOCUMENTS CONSIDERED TO BE RELEVANT <table border="1"> <thead> <tr> <th>Category*</th> <th>Citation of document, with indication, where appropriate, of the relevant passages</th> <th>Relevant to claim No.</th> </tr> </thead> <tbody> <tr> <td>A</td> <td>US 2007/083045 A1 (DI FRANCESCO MARIA E [IT] ET AL) 12 April 2007 (2007-04-12) page 1, paragraph [0001];; compounds</td> <td>1-49</td> </tr> <tr> <td>X</td> <td> WO 2005/123680 A1 (SQUIBB BRISTOL MYERS CO [US]; CORTE JAMES [US]; HANGELAND JON [US]; QU) 29 December 2005 (2005-12-29) compounds of table 1 with R being substituted pyridine; compounds of table 2 with R11 being benzyl or derivatives thereof; page 1, line 3 - page 1, line 15 </td> <td>1,2,4, 10-12, 15-22, 26,35, 41,42,47</td> </tr> </tbody> </table>			Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.	A	US 2007/083045 A1 (DI FRANCESCO MARIA E [IT] ET AL) 12 April 2007 (2007-04-12) page 1, paragraph [0001];; compounds	1-49	X	WO 2005/123680 A1 (SQUIBB BRISTOL MYERS CO [US]; CORTE JAMES [US]; HANGELAND JON [US]; QU) 29 December 2005 (2005-12-29) compounds of table 1 with R being substituted pyridine; compounds of table 2 with R11 being benzyl or derivatives thereof; page 1, line 3 - page 1, line 15	1,2,4, 10-12, 15-22, 26,35, 41,42,47
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A	US 2007/083045 A1 (DI FRANCESCO MARIA E [IT] ET AL) 12 April 2007 (2007-04-12) page 1, paragraph [0001];; compounds	1-49									
X	WO 2005/123680 A1 (SQUIBB BRISTOL MYERS CO [US]; CORTE JAMES [US]; HANGELAND JON [US]; QU) 29 December 2005 (2005-12-29) compounds of table 1 with R being substituted pyridine; compounds of table 2 with R11 being benzyl or derivatives thereof; page 1, line 3 - page 1, line 15	1,2,4, 10-12, 15-22, 26,35, 41,42,47									
☐ Further documents are listed in the continuation of Box C. ☒ See patent family annex.											
* Special categories of cited documents : <table> <tr> <td> "A" document defining the general state of the art which is not considered to be of particular relevance "E" earlier application or patent but published on or after the international filing date "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified) "O" document referring to an oral disclosure, use, exhibition or other means "P" document published prior to the international filing date but later than the priority date claimed </td> <td> "T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention "X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone "Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art "&" document member of the same patent family </td> </tr> </table>			"A" document defining the general state of the art which is not considered to be of particular relevance "E" earlier application or patent but published on or after the international filing date "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified) "O" document referring to an oral disclosure, use, exhibition or other means "P" document published prior to the international filing date but later than the priority date claimed	"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention "X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone "Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art "&" document member of the same patent family							
"A" document defining the general state of the art which is not considered to be of particular relevance "E" earlier application or patent but published on or after the international filing date "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified) "O" document referring to an oral disclosure, use, exhibition or other means "P" document published prior to the international filing date but later than the priority date claimed	"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention "X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone "Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art "&" document member of the same patent family										
Date of the actual completion of the international search		Date of mailing of the international search report									
12 September 2012		19/09/2012									
Name and mailing address of the ISA/ European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016		Authorized officer Schmid, Arnold									

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No

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