

PHARMACOLOGICAL CORRECTORS OF RHODOPSIN AND USES THEREOF

CROSS-REFERENCE

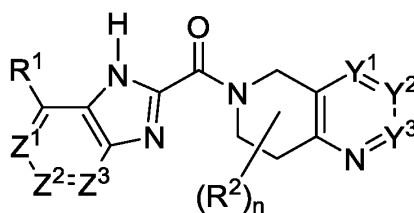
[0001] This application claims benefit of U.S. Provisional Patent Application No. 63/597,275 filed on November 8, 2023 and U.S. Provisional Patent Application No. 63/712,969 filed on October 28, 2024, each of which is incorporated herein by reference in its entirety.

BACKGROUND OF THE INVENTION

[0002] Autosomal dominant retinitis pigmentosa (adRP) is a progressive blindness disease with over 10,000 patients in the U.S. and Europe alone. Misfolding mutations of Rhodopsin constitute the most common cause of adRP. There is currently no approved pharmacologic treatment for rhodopsin-mediated autosomal dominant retinitis pigmentosa (RHO-adRP). Therefore, an approved RHO-adRP therapy would address an important unmet medical need.

SUMMARY OF THE INVENTION

[0003] In one aspect, described herein is a compound of Formula (I), or a pharmaceutically acceptable salt or solvate thereof:



Formula (I);

wherein:

Y¹, Y², and Y³ are each independently C(R³) or N, wherein at least one of Y² and Y³ is C(R³);

Z¹, Z², and Z³ are each independently C(R⁴) or N, wherein at least one of Z¹, Z², and Z³ is C(R⁴);

R¹ is selected from hydrogen, halogen, -CN, -OR¹⁰, -SR¹⁰, -N(R¹⁰)(R¹¹), -C(O)OR¹⁰, -OC(O)N(R¹⁰)(R¹¹), -N(R¹²)C(O)N(R¹⁰)(R¹¹), -N(R¹²)C(O)OR¹³, -N(R¹²)S(O)₂R¹³, -C(O)R¹³, -S(O)R¹³, -OC(O)R¹³, -C(O)N(R¹⁰)(R¹¹), -N(R¹²)C(O)R¹³, -S(O)₂R¹³, -S(O)₂N(R¹⁰)(R¹¹), -S(=O)(=NH)N(R¹⁰)(R¹¹), C₁₋₆alkyl, C₁₋₆haloalkyl, C₂₋₆alkenyl, C₂₋₆alkynyl, C₃₋₆cycloalkyl, C₂₋₉heterocycloalkyl, C₆₋₁₀aryl, and C₁₋₉heteroaryl, wherein C₁₋₆alkyl, C₁₋₆haloalkyl, C₂₋₆alkenyl, C₂₋₆alkynyl, C₃₋₆cycloalkyl, C₂₋₉heterocycloalkyl, C₆₋₁₀aryl, and C₁₋₉heteroaryl are optionally substituted with 1-5 R^{5a} groups;

each R² is independently selected from halogen, -CN, -OR¹⁰, -SR¹⁰, -N(R¹⁰)(R¹¹), C₁₋₆alkyl, C₁₋₆haloalkyl, C₂₋₆alkenyl, C₂₋₆alkynyl, C₃₋₆cycloalkyl, C₂₋₉heterocycloalkyl, C₆₋₁₀aryl, and C₁₋₉heteroaryl, wherein C₁₋₆alkyl, C₁₋₆haloalkyl, C₂₋₆alkenyl, C₂₋₆alkynyl, C₃₋₆cycloalkyl, C₂₋₉heterocycloalkyl, C₆₋₁₀aryl, and C₁₋₉heteroaryl are optionally substituted with 1-5 R^{5b} groups;

each R³ is independently selected from hydrogen, halogen, -CN, -SR¹⁰, -N(R¹⁰)(R¹¹), C₁₋₆alkyl, C₁₋₆haloalkyl, C₁₋₆alkoxy, C₂₋₆alkenyl, C₂₋₆alkynyl, C₃₋₆cycloalkyl, C₂₋₉heterocycloalkyl, C₆₋₁₀aryl, and C₁₋₉heteroaryl, wherein C₁₋₆alkyl, C₁₋₆haloalkyl, C₁₋₆alkoxy, C₂₋₆alkenyl, C₂₋₆alkynyl, C₃₋₆cycloalkyl, C₂₋₉heterocycloalkyl, C₆₋₁₀aryl, and C₁₋₉heteroaryl are optionally substituted with 1-5 R^{5c} groups;

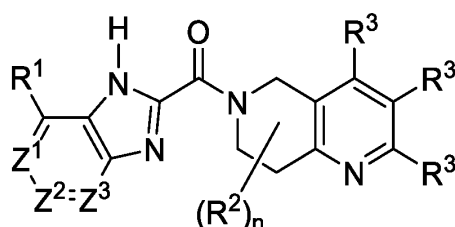
each R⁴ is independently selected from hydrogen, halogen, -CN, -OR¹⁰, -SR¹⁰, -N(R¹⁰)(R¹¹), C₁₋₆alkyl, C₁₋₆haloalkyl, C₂₋₆alkenyl, C₂₋₆alkynyl, C₃₋₆cycloalkyl, C₂₋₉heterocycloalkyl, C₆₋₁₀aryl, and C₁₋₉heteroaryl, wherein C₁₋₆alkyl, C₁₋₆haloalkyl, C₂₋₆alkenyl, C₂₋₆alkynyl, C₃₋₆cycloalkyl, C₂₋₉heterocycloalkyl, C₆₋₁₀aryl, and C₁₋₉heteroaryl are optionally substituted with 1-5 R^{5d} groups;

each R^{5a}, R^{5b}, R^{5c}, and R^{5d} is each independently selected from halogen, oxo, -CN, C₁₋₆alkyl, C₁₋₆haloalkyl, C₂₋₆alkenyl, C₂₋₆alkynyl, C₃₋₆cycloalkyl, -CH₂-C₃₋₆cycloalkyl, C₂₋₉heterocycloalkyl, -CH₂-C₂₋₉heterocycloalkyl, C₆₋₁₀aryl, -CH₂-C₆₋₁₀aryl, C₁₋₉heteroaryl, -CH₂-C₁₋₉heteroaryl, -OR¹⁰, -SR¹⁰, -N(R¹⁰)(R¹¹), -C(O)OR¹⁰, -OC(O)N(R¹⁰)(R¹¹), -N(R¹²)C(O)N(R¹⁰)(R¹¹), -N(R¹²)C(O)OR¹³, -N(R¹²)S(O)₂R¹³, -C(O)R¹³, -S(O)R¹³, -OC(O)R¹³, -C(O)N(R¹⁰)(R¹¹), -C(O)C(O)N(R¹⁰)(R¹¹), -N(R¹²)C(O)R¹³, -S(O)₂R¹³, -S(O)₂N(R¹⁰)(R¹¹), -S(=O)(=NH)N(R¹⁰)(R¹¹), -C(=NOR¹¹)R¹³, -CH₂C(O)N(R¹⁰)(R¹¹), -CH₂N(R¹²)C(O)R¹³, -CH₂S(O)₂R¹³, and -CH₂S(O)₂N(R¹⁰)(R¹¹), wherein C₁₋₆alkyl, C₁₋₆haloalkyl, C₂₋₆alkenyl, C₂₋₆alkynyl, C₃₋₆cycloalkyl, -CH₂-C₃₋₆cycloalkyl, C₂₋₉heterocycloalkyl, -CH₂-C₂₋₉heterocycloalkyl, C₆₋₁₀aryl, -CH₂-C₆₋₁₀aryl, C₁₋₉heteroaryl, -CH₂-C₁₋₉heteroaryl are optionally substituted with one, two, or three groups selected from halogen, -CN, C₁₋₆alkyl, C₁₋₆haloalkyl, C₃₋₆cycloalkyl, C₂₋₉heterocycloalkyl, C₆₋₁₀aryl, C₁₋₉heteroaryl, -OR¹⁰, and -N(R¹⁰)(R¹¹);

each R¹⁰ is independently selected from hydrogen, C₁₋₆alkyl, C₁₋₆haloalkyl, C₂₋₆alkenyl, C₂₋₆alkynyl, C₃₋₆cycloalkyl, C₂₋₉heterocycloalkyl, C₆₋₁₀aryl, and C₁₋₉heteroaryl, wherein C₁₋₆alkyl, C₂₋₆alkenyl, C₂₋₆alkynyl, C₃₋₆cycloalkyl, C₂₋₉heterocycloalkyl, C₆₋₁₀aryl, and C₁₋₉heteroaryl are optionally substituted with one, two, or three groups selected from halogen, -CN, hydroxy, C₁₋₆alkyl, C₁₋₆haloalkyl, C₁₋₆alkoxy, C₃₋₆cycloalkyl, C₂₋₉heterocycloalkyl, C₆₋₁₀aryl, and C₁₋₉heteroaryl;

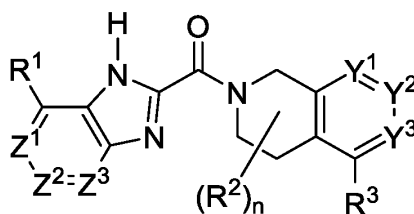
each R^{11} is independently selected from hydrogen, C_{1-6} alkyl, and C_{1-6} haloalkyl;
 each R^{12} is independently selected from hydrogen, C_{1-6} alkyl, and C_{1-6} haloalkyl;
 each R^{13} is independently selected C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-6} cycloalkyl, C_{2-9} heterocycloalkyl, C_{6-10} aryl, and C_{1-9} heteroaryl, wherein C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-6} cycloalkyl, C_{2-9} heterocycloalkyl, C_{6-10} aryl, and C_{1-9} heteroaryl are optionally substituted with one, two, or three groups selected from halogen, -CN, hydroxy, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} alkoxy, C_{3-6} cycloalkyl, C_{2-9} heterocycloalkyl, C_{6-10} aryl, and C_{1-9} heteroaryl; and
 n is 0, 1, 2, 3, or 4.

[0004] In some embodiments is a compound of Formula (I), or a pharmaceutically acceptable salt or solvate thereof, having the structure of Formula (Ia):



Formula (Ia).

[0005] In another aspect, described herein is a compound of Formula (II), or a pharmaceutically acceptable salt or solvate thereof:



Formula (II);

wherein:

Y^1 , Y^2 , and Y^3 are each independently $C(R^3)$ or N, wherein at least one of Y^1 , Y^2 , and Y^3 is $C(R^3)$;

Z^1 , Z^2 , and Z^3 are each independently $C(R^4)$ or N, wherein at least one of Z^1 , Z^2 , and Z^3 is $C(R^4)$;

R^1 is selected from halogen, -CN, -OR¹⁰, -SR¹⁰, -N(R¹⁰)(R¹¹), C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-6} cycloalkyl, C_{2-9} heterocycloalkyl, C_{6-10} aryl, and C_{1-9} heteroaryl, wherein C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-6} cycloalkyl, C_{2-9}

₉heterocycloalkyl, C₆₋₁₀aryl, and C₁₋₉heteroaryl are optionally substituted with 1-5 R^{5a} groups;

each R² is independently selected from halogen, -CN, -OR¹⁰, -SR¹⁰, -N(R¹⁰)(R¹¹), C₁₋₆alkyl, C₁₋₆haloalkyl, C₂₋₆alkenyl, C₂₋₆alkynyl, C₃₋₆cycloalkyl, C₂₋₉heterocycloalkyl, C₆₋₁₀aryl, and C₁₋₉heteroaryl, wherein C₁₋₆alkyl, C₁₋₆haloalkyl, C₂₋₆alkenyl, C₂₋₆alkynyl, C₃₋₆cycloalkyl, C₂₋₉heterocycloalkyl, C₆₋₁₀aryl, and C₁₋₉heteroaryl are optionally substituted with 1-5 R^{5b} groups; or two R² groups on different carbon atoms are taken together to form a bridge that is -CH₂CH₂-;

each R³ is independently selected from hydrogen, halogen, -CN, -SR¹⁰, -N(R¹⁰)(R¹¹), C₁₋₆alkyl, C₁₋₆haloalkyl, C₁₋₆alkoxy, C₂₋₆alkenyl, C₂₋₆alkynyl, C₃₋₆cycloalkyl, C₂₋₉heterocycloalkyl, C₆₋₁₀aryl, and C₁₋₉heteroaryl, wherein C₁₋₆alkyl, C₁₋₆haloalkyl, C₁₋₆alkoxy, C₂₋₆alkenyl, C₂₋₆alkynyl, C₃₋₆cycloalkyl, C₂₋₉heterocycloalkyl, C₆₋₁₀aryl, and C₁₋₉heteroaryl are optionally substituted with 1-5 R^{5c} groups;

each R⁴ is independently selected from hydrogen, halogen, -CN, -OR¹⁰, -SR¹⁰, -N(R¹⁰)(R¹¹), C₁₋₆alkyl, C₁₋₆haloalkyl, C₂₋₆alkenyl, C₂₋₆alkynyl, C₃₋₆cycloalkyl, C₂₋₉heterocycloalkyl, C₆₋₁₀aryl, and C₁₋₉heteroaryl, wherein C₁₋₆alkyl, C₁₋₆haloalkyl, C₂₋₆alkenyl, C₂₋₆alkynyl, C₃₋₆cycloalkyl, C₂₋₉heterocycloalkyl, C₆₋₁₀aryl, and C₁₋₉heteroaryl are optionally substituted with 1-5 R^{5d} groups;

each R^{5a}, R^{5b}, R^{5c}, and R^{5d} is each independently selected from halogen, oxo, -CN, C₁₋₆alkyl, C₁₋₆haloalkyl, C₂₋₆alkenyl, C₂₋₆alkynyl, C₃₋₆cycloalkyl, -CH₂-C₃₋₆cycloalkyl, C₂₋₉heterocycloalkyl, -CH₂-C₂₋₉heterocycloalkyl, C₆₋₁₀aryl, -CH₂-C₆₋₁₀aryl, C₁₋₉heteroaryl, -CH₂-C₁₋₉heteroaryl, -OR¹⁰, -SR¹⁰, -N(R¹⁰)(R¹¹), -C(O)OR¹⁰, -OC(O)N(R¹⁰)(R¹¹), -N(R¹²)C(O)N(R¹⁰)(R¹¹), -N(R¹²)C(O)OR¹³, -N(R¹²)S(O)₂R¹³, -C(O)R¹³, -S(O)R¹³, -OC(O)R¹³, -C(O)N(R¹⁰)(R¹¹), -C(O)C(O)N(R¹⁰)(R¹¹), -N(R¹²)C(O)R¹³, -S(O)₂R¹³, -S(O)₂N(R¹⁰)(R¹¹), -S(=O)(=NH)N(R¹⁰)(R¹¹), -C(=NOR¹¹)R¹³, -CH₂C(O)N(R¹⁰)(R¹¹), -CH₂N(R¹²)C(O)R¹³, -CH₂S(O)₂R¹³, and -CH₂S(O)₂N(R¹⁰)(R¹¹), wherein C₁₋₆alkyl, C₁₋₆haloalkyl, C₂₋₆alkenyl, C₂₋₆alkynyl, C₃₋₆cycloalkyl, -CH₂-C₃₋₆cycloalkyl, C₂₋₉heterocycloalkyl, -CH₂-C₂₋₉heterocycloalkyl, C₆₋₁₀aryl, -CH₂-C₆₋₁₀aryl, C₁₋₉heteroaryl, -CH₂-C₁₋₉heteroaryl are optionally substituted with one, two, or three groups selected from halogen, -CN, C₁₋₆alkyl, C₁₋₆haloalkyl, C₃₋₆cycloalkyl, C₂₋₉heterocycloalkyl, C₆₋₁₀aryl, C₁₋₉heteroaryl, -OR¹⁰, and -N(R¹⁰)(R¹¹);

each R¹⁰ is independently selected from hydrogen, C₁₋₆alkyl, C₁₋₆haloalkyl, C₂₋₆alkenyl, C₂₋₆alkynyl, C₃₋₆cycloalkyl, C₂₋₉heterocycloalkyl, C₆₋₁₀aryl, and C₁₋₉heteroaryl, wherein C₁₋₆alkyl, C₂₋₆alkenyl, C₂₋₆alkynyl, C₃₋₆cycloalkyl, C₂₋₉heterocycloalkyl, C₆₋₁₀aryl, and C₁₋

₉heteroaryl are optionally substituted with one, two, or three groups selected from halogen, -CN, hydroxy, C₁₋₆alkyl, C₁₋₆haloalkyl, C₁₋₆alkoxy, C₃₋₆cycloalkyl, C₂₋

₉heterocycloalkyl, C₆₋₁₀aryl, and C₁₋₉heteroaryl;

each R¹¹ is independently selected from hydrogen, C₁₋₆alkyl, and C₁₋₆haloalkyl;

each R¹² is independently selected from hydrogen, C₁₋₆alkyl, and C₁₋₆haloalkyl;

each R¹³ is independently selected C₁₋₆alkyl, C₂₋₆alkenyl, C₂₋₆alkynyl, C₃₋₆cycloalkyl, C₂₋

₉heterocycloalkyl, C₆₋₁₀aryl, and C₁₋₉heteroaryl, wherein C₁₋₆alkyl, C₂₋₆alkenyl, C₂₋

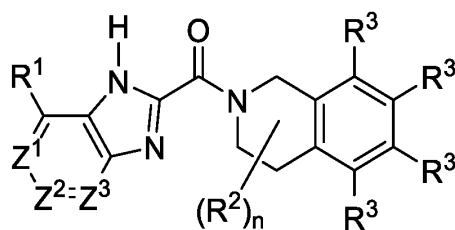
alkynyl, C₃₋₆cycloalkyl, C₂₋₉heterocycloalkyl, C₆₋₁₀aryl, and C₁₋₉heteroaryl are optionally substituted with one, two, or three groups selected from halogen, -CN, hydroxy, C₁₋

alkyl, C₁₋₆haloalkyl, C₁₋₆alkoxy, C₃₋₆cycloalkyl, C₂₋₉heterocycloalkyl, C₆₋₁₀aryl, and C₁₋

₉heteroaryl; and

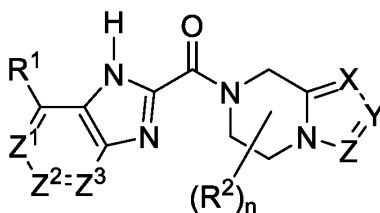
n is 1, 2, 3, or 4.

[0006] In some embodiments is a compound of Formula (II), or a pharmaceutically acceptable salt or solvate thereof, having the structure of Formula (IIa):



Formula (IIa).

[0007] In another aspect, described herein is a compound of Formula (III), or a pharmaceutically acceptable salt or solvate thereof:



Formula (III);

wherein:

X, Y and Z are each independently C(R³) or N, wherein at least one of Y and Z is C(R³);

Z¹, Z², and Z³ are each independently C(R⁴) or N, wherein at least one of Z¹, Z², and Z³ is C(R⁴);

R¹ is selected from halogen, -CN, -OR¹⁰, -SR¹⁰, -N(R¹⁰)(R¹¹), C₁₋₆alkyl, C₁₋₆haloalkyl, C₂₋

alkenyl, C₂₋₆alkynyl, C₃₋₆cycloalkyl, C₆₋₁₀aryl, and C₁₋₉heteroaryl, wherein C₁₋₆alkyl, C₁₋

₆haloalkyl, C₂₋₆alkenyl, C₂₋₆alkynyl, C₃₋₆cycloalkyl, C₆₋₁₀aryl, and C₁₋₉heteroaryl are optionally substituted with 1-5 R^{5a} groups;

each R² is independently selected from halogen, -CN, -OR¹⁰, -SR¹⁰, -N(R¹⁰)(R¹¹), C₁₋₆alkyl, C₁₋₆haloalkyl, C₂₋₆alkenyl, C₂₋₆alkynyl, C₃₋₆cycloalkyl, C₂₋₉heterocycloalkyl, C₆₋₁₀aryl, and C₁₋₉heteroaryl, wherein C₁₋₆alkyl, C₁₋₆haloalkyl, C₂₋₆alkenyl, C₂₋₆alkynyl, C₃₋₆cycloalkyl, C₂₋₉heterocycloalkyl, C₆₋₁₀aryl, and C₁₋₉heteroaryl are optionally substituted with 1-5 R^{5b} groups;

each R³ is independently selected from hydrogen, halogen, -CN, -SR¹⁰, -N(R¹⁰)(R¹¹), C₁₋₆alkyl, C₁₋₆haloalkyl, C₁₋₆alkoxy, C₂₋₆alkenyl, C₂₋₆alkynyl, C₃₋₆cycloalkyl, C₂₋₉heterocycloalkyl, C₆₋₁₀aryl, and C₁₋₉heteroaryl, wherein C₁₋₆alkyl, C₁₋₆haloalkyl, C₁₋₆alkoxy, C₂₋₆alkenyl, C₂₋₆alkynyl, C₃₋₆cycloalkyl, C₂₋₉heterocycloalkyl, C₆₋₁₀aryl, and C₁₋₉heteroaryl are optionally substituted with 1-5 R^{5c} groups;

each R⁴ is independently selected from hydrogen, halogen, -CN, -OR¹⁰, -SR¹⁰, -N(R¹⁰)(R¹¹), C₁₋₆alkyl, C₁₋₆haloalkyl, C₂₋₆alkenyl, C₂₋₆alkynyl, C₃₋₆cycloalkyl, C₂₋₉heterocycloalkyl, C₆₋₁₀aryl, and C₁₋₉heteroaryl, wherein C₁₋₆alkyl, C₁₋₆haloalkyl, C₂₋₆alkenyl, C₂₋₆alkynyl, C₃₋₆cycloalkyl, C₂₋₉heterocycloalkyl, C₆₋₁₀aryl, and C₁₋₉heteroaryl are optionally substituted with 1-5 R^{5d} groups;

each R^{5a}, R^{5b}, R^{5c}, and R^{5d} is each independently selected from halogen, oxo, -CN, C₁₋₆alkyl, C₁₋₆haloalkyl, C₂₋₆alkenyl, C₂₋₆alkynyl, C₃₋₆cycloalkyl, -CH₂-C₃₋₆cycloalkyl, C₂₋₉heterocycloalkyl, -CH₂-C₂₋₉heterocycloalkyl, C₆₋₁₀aryl, -CH₂-C₆₋₁₀aryl, C₁₋₉heteroaryl, -CH₂-C₁₋₉heteroaryl, -OR¹⁰, -SR¹⁰, -N(R¹⁰)(R¹¹), -C(O)OR¹⁰, -OC(O)N(R¹⁰)(R¹¹), -N(R¹²)C(O)N(R¹⁰)(R¹¹), -N(R¹²)C(O)OR¹³, -N(R¹²)S(O)₂R¹³, -C(O)R¹³, -S(O)R¹³, -OC(O)R¹³, -C(O)N(R¹⁰)(R¹¹), -C(O)C(O)N(R¹⁰)(R¹¹), -N(R¹²)C(O)R¹³, -S(O)₂R¹³, -S(O)₂N(R¹⁰)(R¹¹), -S(=O)(=NH)N(R¹⁰)(R¹¹), -C(=NOR¹¹)R¹³, -CH₂C(O)N(R¹⁰)(R¹¹), -CH₂N(R¹²)C(O)R¹³, -CH₂S(O)₂R¹³, and -CH₂S(O)₂N(R¹⁰)(R¹¹), wherein C₁₋₆alkyl, C₁₋₆haloalkyl, C₂₋₆alkenyl, C₂₋₆alkynyl, C₃₋₆cycloalkyl, -CH₂-C₃₋₆cycloalkyl, C₂₋₉heterocycloalkyl, -CH₂-C₂₋₉heterocycloalkyl, C₆₋₁₀aryl, -CH₂-C₆₋₁₀aryl, C₁₋₉heteroaryl, -CH₂-C₁₋₉heteroaryl are optionally substituted with one, two, or three groups selected from halogen, -CN, C₁₋₆alkyl, C₁₋₆haloalkyl, C₃₋₆cycloalkyl, C₂₋₉heterocycloalkyl, C₆₋₁₀aryl, C₁₋₉heteroaryl, -OR¹⁰, and -N(R¹⁰)(R¹¹);

each R¹⁰ is independently selected from hydrogen, C₁₋₆alkyl, C₁₋₆haloalkyl, C₂₋₆alkenyl, C₂₋₆alkynyl, C₃₋₆cycloalkyl, C₂₋₉heterocycloalkyl, C₆₋₁₀aryl, and C₁₋₉heteroaryl, wherein C₁₋₆alkyl, C₂₋₆alkenyl, C₂₋₆alkynyl, C₃₋₆cycloalkyl, C₂₋₉heterocycloalkyl, C₆₋₁₀aryl, and C₁₋₉heteroaryl are optionally substituted with one, two, or three groups selected from

halogen, -CN, hydroxy, C₁₋₆alkyl, C₁₋₆haloalkyl, C₁₋₆alkoxy, C₃₋₆cycloalkyl, C₂₋₉heterocycloalkyl, C₆₋₁₀aryl, and C₁₋₉heteroaryl;

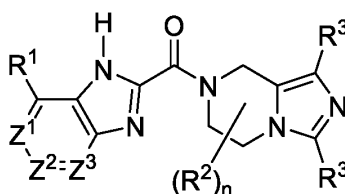
each R¹¹ is independently selected from hydrogen, C₁₋₆alkyl, and C₁₋₆haloalkyl;

each R¹² is independently selected from hydrogen, C₁₋₆alkyl, and C₁₋₆haloalkyl;

each R¹³ is independently selected C₁₋₆alkyl, C₂₋₆alkenyl, C₂₋₆alkynyl, C₃₋₆cycloalkyl, C₂₋₉heterocycloalkyl, C₆₋₁₀aryl, and C₁₋₉heteroaryl, wherein C₁₋₆alkyl, C₂₋₆alkenyl, C₂₋₆alkynyl, C₃₋₆cycloalkyl, C₂₋₉heterocycloalkyl, C₆₋₁₀aryl, and C₁₋₉heteroaryl are optionally substituted with one, two, or three groups selected from halogen, -CN, hydroxy, C₁₋₆alkyl, C₁₋₆haloalkyl, C₁₋₆alkoxy, C₃₋₆cycloalkyl, C₂₋₉heterocycloalkyl, C₆₋₁₀aryl, and C₁₋₉heteroaryl; and

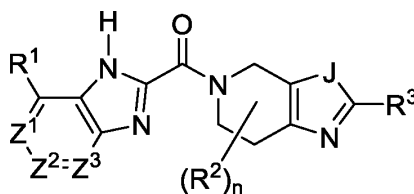
n is 0, 1, 2, 3, or 4.

[0008] In some embodiments is a compound of Formula (III), or a pharmaceutically acceptable salt or solvate thereof, having the structure of Formula (IIIa):



Formula (IIIa).

[0009] In another aspect, described herein is a compound of Formula (IV), or a pharmaceutically acceptable salt or solvate thereof:



Formula (IV);

wherein:

Z¹, Z², and Z³ are each independently C(R⁴) or N, wherein at least one of Z¹, Z², and Z³ is C(R⁴);

J is O or S;

R¹ is selected from hydrogen, halogen, -CN, -OR¹⁰, -SR¹⁰, -N(R¹⁰)(R¹¹), C₁₋₆alkyl, C₁₋₆haloalkyl, C₂₋₆alkenyl, C₂₋₆alkynyl, C₃₋₆cycloalkyl, C₂₋₉heterocycloalkyl, C₆₋₁₀aryl, and C₁₋₉heteroaryl, wherein C₁₋₆alkyl, C₁₋₆haloalkyl, C₂₋₆alkenyl, C₂₋₆alkynyl, C₃₋₆cycloalkyl,

C₂₋₉heterocycloalkyl, C₆₋₁₀aryl, and C₁₋₉heteroaryl are optionally substituted with 1-5 R^{5a} groups;

each R² is independently selected from halogen, -CN, -OR¹⁰, -SR¹⁰, -N(R¹⁰)(R¹¹), C₁₋₆alkyl, C₁₋₆haloalkyl, C₂₋₆alkenyl, C₂₋₆alkynyl, C₃₋₆cycloalkyl, C₂₋₉heterocycloalkyl, C₆₋₁₀aryl, and C₁₋₉heteroaryl, wherein C₁₋₆alkyl, C₁₋₆haloalkyl, C₂₋₆alkenyl, C₂₋₆alkynyl, C₃₋₆cycloalkyl, C₂₋₉heterocycloalkyl, C₆₋₁₀aryl, and C₁₋₉heteroaryl are optionally substituted with 1-5 R^{5b} groups;

R³ is selected from hydrogen, halogen, -CN, -SR¹⁰, -N(R¹⁰)(R¹¹), C₁₋₆alkyl, C₁₋₆haloalkyl, C₁₋₆alkoxy, C₂₋₆alkenyl, C₂₋₆alkynyl, C₃₋₆cycloalkyl, C₂₋₉heterocycloalkyl, C₆₋₁₀aryl, and C₁₋₉heteroaryl, wherein C₁₋₆alkyl, C₁₋₆haloalkyl, C₁₋₆alkoxy, C₂₋₆alkenyl, C₂₋₆alkynyl, C₃₋₆cycloalkyl, C₂₋₉heterocycloalkyl, C₆₋₁₀aryl, and C₁₋₉heteroaryl are optionally substituted with 1-5 R^{5c} groups;

each R⁴ is independently selected from hydrogen, halogen, -CN, -OR¹⁰, -SR¹⁰, -N(R¹⁰)(R¹¹), C₁₋₆alkyl, C₁₋₆haloalkyl, C₂₋₆alkenyl, C₂₋₆alkynyl, C₃₋₆cycloalkyl, C₂₋₉heterocycloalkyl, C₆₋₁₀aryl, and C₁₋₉heteroaryl, wherein C₁₋₆alkyl, C₁₋₆haloalkyl, C₂₋₆alkenyl, C₂₋₆alkynyl, C₃₋₆cycloalkyl, C₂₋₉heterocycloalkyl, C₆₋₁₀aryl, and C₁₋₉heteroaryl are optionally substituted with 1-5 R^{5d} groups;

each R^{5a}, R^{5b}, R^{5c}, and R^{5d} is each independently selected from halogen, oxo, -CN, C₁₋₆alkyl, C₁₋₆haloalkyl, C₂₋₆alkenyl, C₂₋₆alkynyl, C₃₋₆cycloalkyl, -CH₂-C₃₋₆cycloalkyl, C₂₋₉heterocycloalkyl, -CH₂-C₂₋₉heterocycloalkyl, C₆₋₁₀aryl, -CH₂-C₆₋₁₀aryl, C₁₋₉heteroaryl, -CH₂-C₁₋₉heteroaryl, -OR¹⁰, -SR¹⁰, -N(R¹⁰)(R¹¹), -C(O)OR¹⁰, -OC(O)N(R¹⁰)(R¹¹), -N(R¹²)C(O)N(R¹⁰)(R¹¹), -N(R¹²)C(O)OR¹³, -N(R¹²)S(O)₂R¹³, -C(O)R¹³, -S(O)R¹³, -OC(O)R¹³, -C(O)N(R¹⁰)(R¹¹), -C(O)C(O)N(R¹⁰)(R¹¹), -N(R¹²)C(O)R¹³, -S(O)₂R¹³, -S(O)₂N(R¹⁰)(R¹¹), -S(=O)(=NH)N(R¹⁰)(R¹¹), -C(=NOR¹¹)R¹³, -CH₂C(O)N(R¹⁰)(R¹¹), -CH₂N(R¹²)C(O)R¹³, -CH₂S(O)₂R¹³, and -CH₂S(O)₂N(R¹⁰)(R¹¹), wherein C₁₋₆alkyl, C₁₋₆haloalkyl, C₂₋₆alkenyl, C₂₋₆alkynyl, C₃₋₆cycloalkyl, -CH₂-C₃₋₆cycloalkyl, C₂₋₉heterocycloalkyl, -CH₂-C₂₋₉heterocycloalkyl, C₆₋₁₀aryl, -CH₂-C₆₋₁₀aryl, C₁₋₉heteroaryl, -CH₂-C₁₋₉heteroaryl are optionally substituted with one, two, or three groups selected from halogen, -CN, C₁₋₆alkyl, C₁₋₆haloalkyl, C₃₋₆cycloalkyl, C₂₋₉heterocycloalkyl, C₆₋₁₀aryl, C₁₋₉heteroaryl, -OR¹⁰, and -N(R¹⁰)(R¹¹);

each R¹⁰ is independently selected from hydrogen, C₁₋₆alkyl, C₁₋₆haloalkyl, C₂₋₆alkenyl, C₂₋₆alkynyl, C₃₋₆cycloalkyl, C₂₋₉heterocycloalkyl, C₆₋₁₀aryl, and C₁₋₉heteroaryl, wherein C₁₋₆alkyl, C₂₋₆alkenyl, C₂₋₆alkynyl, C₃₋₆cycloalkyl, C₂₋₉heterocycloalkyl, C₆₋₁₀aryl, and C₁₋₉heteroaryl are optionally substituted with one, two, or three groups selected from

halogen, -CN, hydroxy, C₁₋₆alkyl, C₁₋₆haloalkyl, C₁₋₆alkoxy, C₃₋₆cycloalkyl, C₂₋₉heterocycloalkyl, C₆₋₁₀aryl, and C₁₋₉heteroaryl;

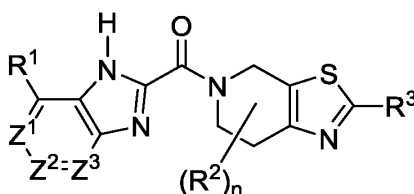
each R¹¹ is independently selected from hydrogen, C₁₋₆alkyl, and C₁₋₆haloalkyl;

each R¹² is independently selected from hydrogen, C₁₋₆alkyl, and C₁₋₆haloalkyl;

each R¹³ is independently selected C₁₋₆alkyl, C₂₋₆alkenyl, C₂₋₆alkynyl, C₃₋₆cycloalkyl, C₂₋₉heterocycloalkyl, C₆₋₁₀aryl, and C₁₋₉heteroaryl, wherein C₁₋₆alkyl, C₂₋₆alkenyl, C₂₋₆alkynyl, C₃₋₆cycloalkyl, C₂₋₉heterocycloalkyl, C₆₋₁₀aryl, and C₁₋₉heteroaryl are optionally substituted with one, two, or three groups selected from halogen, -CN, hydroxy, C₁₋₆alkyl, C₁₋₆haloalkyl, C₁₋₆alkoxy, C₃₋₆cycloalkyl, C₂₋₉heterocycloalkyl, C₆₋₁₀aryl, and C₁₋₉heteroaryl; and

n is 0, 1, 2, 3, or 4.

[0010] In some embodiments is a compound of Formula (IV), or a pharmaceutically acceptable salt or solvate thereof, having the structure of Formula (IVa):



Formula (IVa).

[0011] In some embodiments is a compound of Formula (I), (Ia), (II), (IIa), (II), (IIIa), (IV), or (IVa), or a pharmaceutically acceptable salt or solvate thereof, wherein each R³ is independently selected from hydrogen, halogen, -CN, -N(R¹⁰)(R¹¹), C₁₋₆alkyl, C₁₋₆haloalkyl, C₁₋₆alkoxy, and C₃₋₆cycloalkyl, wherein C₁₋₆alkyl, C₁₋₆haloalkyl, C₁₋₆alkoxy, and C₃₋₆cycloalkyl are optionally substituted with 1-5 R^{5c} groups. In some embodiments is a compound of Formula (I), (Ia), (II), (IIa), (II), (IIIa), (IV), or (IVa), or a pharmaceutically acceptable salt or solvate thereof, wherein each R³ is independently selected from hydrogen, halogen, -CN, C₁₋₆alkyl, C₁₋₆haloalkyl, and C₁₋₆alkoxy, wherein C₁₋₆alkyl, C₁₋₆haloalkyl, and C₁₋₆alkoxy are optionally substituted with 1-5 R^{5c} groups. In some embodiments is a compound of Formula (I), (Ia), (II), (IIa), (II), (IIIa), (IV), or (IVa), or a pharmaceutically acceptable salt or solvate thereof, wherein each R³ is independently selected from hydrogen, halogen, -CN, C₁₋₆alkyl, C₁₋₆haloalkyl, and C₁₋₆alkoxy, wherein C₁₋₆alkyl, C₁₋₆haloalkyl, and C₁₋₆alkoxy are optionally substituted with 1-3 R^{5c} groups. In some embodiments is a compound of Formula (I), (Ia), (II), (IIa), (II), (IIIa), (IV), or (IVa), or a pharmaceutically acceptable salt or solvate thereof, wherein each R³ is independently selected from hydrogen, halogen, -CN, unsubstituted C₁₋₆alkyl, -CF₃, and -OCH₃. In some embodiments

is a compound of Formula (I), (Ia), (II), (IIa), (II), (IIIa), (IV), or (IVa), or a pharmaceutically acceptable salt or solvate thereof, wherein each R^3 is independently selected from hydrogen, halogen, and $-CH_3$. In some embodiments is a compound of Formula (I), (Ia), (II), (IIa), (II), (IIIa), (IV), or (IVa), or a pharmaceutically acceptable salt or solvate thereof, wherein each R^3 is hydrogen. In some embodiments is a compound of Formula (I), (Ia), (II), (IIa), (II), (IIIa), (IV), or (IVa), or a pharmaceutically acceptable salt or solvate thereof, wherein each R^2 is independently selected from $-OR^{10}$, C_{1-6} alkyl, and C_{1-6} haloalkyl, wherein C_{1-6} alkyl and C_{1-6} haloalkyl are optionally substituted with 1-5 R^{5b} groups. In some embodiments is a compound of Formula (I), (Ia), (II), (IIa), (II), (IIIa), (IV), or (IVa), or a pharmaceutically acceptable salt or solvate thereof, wherein each R^2 is independently selected from unsubstituted C_{1-6} alkyl. In some embodiments is a compound of Formula (I), (Ia), (II), (IIa), (II), (IIIa), (IV), or (IVa), or a pharmaceutically acceptable salt or solvate thereof, wherein each R^2 is $-CH_3$. In some embodiments is a compound of Formula (I), (Ia), (II), (IIa), (II), (IIIa), (IV), or (IVa), or a pharmaceutically acceptable salt or solvate thereof, wherein n is 1. In some embodiments is a compound of Formula (I), (Ia), (II), (IIa), (II), (IIIa), (IV), or (IVa), or a pharmaceutically acceptable salt or solvate thereof, wherein n is 2. In some embodiments is a compound of Formula (I), (Ia), (II), (IIa), (II), (IIIa), (IV), or (IVa), or a pharmaceutically acceptable salt or solvate thereof, wherein n is 0. In some embodiments is a compound of Formula (I), (Ia), (II), (IIa), (II), (IIIa), (IV), or (IVa), or a pharmaceutically acceptable salt or solvate thereof, wherein R^1 is selected from halogen, $-CN$, $-OR^{10}$, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{6-10} aryl, and C_{1-9} heteroaryl, wherein C_{1-6} alkyl and C_{1-6} haloalkyl are optionally substituted with 1-5 R^{5a} groups. In some embodiments is a compound of Formula (I), (Ia), (II), (IIa), (II), (IIIa), (IV), or (IVa), or a pharmaceutically acceptable salt or solvate thereof, wherein R^1 is selected from halogen, $-CN$, $-OR^{10}$, C_{1-6} alkyl, and C_{1-6} haloalkyl, wherein C_{1-6} alkyl and C_{1-6} haloalkyl are optionally substituted with 1-5 R^{5a} groups. In some embodiments is a compound of Formula (I), (Ia), (II), (IIa), (II), (IIIa), (IV), or (IVa), or a pharmaceutically acceptable salt or solvate thereof, wherein R^1 is selected from halogen, $-CN$, $-OR^{10}$, unsubstituted C_{1-6} alkyl, and unsubstituted C_{1-6} haloalkyl. In some embodiments is a compound of Formula (I), (Ia), (II), (IIa), (II), (IIIa), (IV), or (IVa), or a pharmaceutically acceptable salt or solvate thereof, wherein R^1 is selected from halogen, $-CN$, $-OH$, $-OCH_3$, $-CH_3$, and $-CF_3$. In some embodiments is a compound of Formula (I), (Ia), (II), (IIa), (II), (IIIa), (IV), or (IVa), or a pharmaceutically acceptable salt or solvate thereof, wherein R^1 is halogen. In some embodiments is a compound of Formula (I), (Ia), (II), (IIa), (II), (IIIa), (IV), or (IVa), or a pharmaceutically acceptable salt or solvate thereof, wherein Z^1 , Z^2 , and Z^3 are each independently $C(R^4)$. In some embodiments is a compound of Formula (I), (Ia), (II), (IIa),

(II), (IIIa), (IV), or (IVa), or a pharmaceutically acceptable salt or solvate thereof, wherein each R^4 is independently selected from hydrogen, halogen, -CN, -OR¹⁰, C₁₋₆alkyl, C₁₋₆haloalkyl, and C₃₋₆cycloalkyl, wherein C₁₋₆alkyl, C₁₋₆haloalkyl, and C₃₋₆cycloalkyl are optionally substituted with 1-5 R^{5d} groups. In some embodiments is a compound of Formula (I), (Ia), (II), (IIa), (II), (IIIa), (IV), or (IVa), or a pharmaceutically acceptable salt or solvate thereof, wherein each R^4 is independently selected from hydrogen, halogen, and unsubstituted C₁₋₆alkyl. In some embodiments is a compound of Formula (I), (Ia), (II), (IIa), (II), (IIIa), (IV), or (IVa), or a pharmaceutically acceptable salt or solvate thereof, wherein each R^4 is independently selected from hydrogen and halogen. In some embodiments is a compound of Formula (I), (Ia), (II), (IIa), (II), (IIIa), (IV), or (IVa), or a pharmaceutically acceptable salt or solvate thereof, wherein each R^4 is hydrogen.

[0012] In another aspect, described herein is a pharmaceutical composition comprising a compound of Formula (I), (Ia), (II), (IIa), (II), (IIIa), (IV), or (IVa), or a pharmaceutically acceptable salt or solvate thereof, and at least one pharmaceutically acceptable excipient.

[0013] In another aspect, described herein is a method of treating autosomal dominant retinitis pigmentosa (adRP) in a patient in need thereof comprising administering to the patient a compound of Formula (I), (Ia), (II), (IIa), (II), (IIIa), (IV), or (IVa), or a pharmaceutically acceptable salt or solvate thereof.

[0014] Any combination of the groups described above for the various variables is contemplated herein. Throughout the specification, groups and substituents thereof are chosen by one skilled in the field to provide stable moieties and compounds.

[0015] Other objects, features and advantages of the compounds, methods and compositions described herein will become apparent from the following detailed description. It should be understood, however, that the detailed description and the specific examples, while indicating specific embodiments, are given by way of illustration only, since various changes and modifications within the spirit and scope of the instant disclosure will become apparent to those skilled in the art from this detailed description.

DETAILED DESCRIPTION OF THE INVENTION

[0016] Autosomal dominant retinitis pigmentosa (adRP) is a progressive blindness disease with no standard of care or approved therapies. Misfolding mutations of Rhodopsin (RHO) constitute the most common cause of adRP. Mutations have toxic gain-of-function effects and most frequently result in RHO misfolding and mistrafficking. Misfolded RHO accumulation

causes cellular stress, which leads to death of photoreceptor cells (rods) and ultimately loss of central vision (cones).

[0017] Described herein are small molecule correctors which prevent or mitigate RHO misfolding, directly addressing the underlying mechanism of disease to restore Rhodopsin trafficking. Properly folded RHO is trafficked to the rod outer segment preventing photoreceptor cell death and preserving vision.

Certain Terminology

[0018] Unless otherwise stated, the following terms used in this application have the definitions given below. The use of the term “including” as well as other forms, such as “include”, “includes,” and “included,” is not limiting. The section headings used herein are for organizational purposes only and are not to be construed as limiting the subject matter described.

[0019] As used herein, C₁-C_x includes C₁-C₂, C₁-C₃ . . . C₁-C_x. By way of example only, a group designated as "C₁-C₄" indicates that there are one to four carbon atoms in the moiety, i.e. groups containing 1 carbon atom, 2 carbon atoms, 3 carbon atoms or 4 carbon atoms. Thus, by way of example only, "C₁-C₄ alkyl" indicates that there are one to four carbon atoms in the alkyl group, i.e., the alkyl group is selected from among methyl, ethyl, propyl, *iso*-propyl, *n*-butyl, *iso*-butyl, *sec*-butyl, and *t*-butyl.

[0020] An “alkyl” group refers to an aliphatic hydrocarbon group. The alkyl group is branched or straight chain. In some embodiments, the “alkyl” group has 1 to 10 carbon atoms, i.e. a C₁-C₁₀alkyl. Whenever it appears herein, a numerical range such as “1 to 10” refers to each integer in the given range; e.g., “1 to 10 carbon atoms” means that the alkyl group consist of 1 carbon atom, 2 carbon atoms, 3 carbon atoms, 4 carbon atoms, 5 carbon atoms, 6 carbon atoms, *etc.*, up to and including 10 carbon atoms, although the present definition also covers the occurrence of the term “alkyl” where no numerical range is designated. In some embodiments, an alkyl is a C₁-C₆alkyl. In one aspect, the alkyl is methyl, ethyl, propyl, *iso*-propyl, *n*-butyl, *iso*-butyl, *sec*-butyl, or *t*-butyl. Typical alkyl groups include, but are in no way limited to, methyl, ethyl, propyl, isopropyl, butyl, isobutyl, *sec*-butyl, tertiary butyl, pentyl, neopentyl, or hexyl.

[0021] An “alkylene” group refers to a divalent alkyl radical. Any of the above mentioned monovalent alkyl groups may be an alkylene by abstraction of a second hydrogen atom from the alkyl. In some embodiments, an alkylene is a C₁-C₆alkylene. In other embodiments, an alkylene is a C₁-C₄alkylene. In certain embodiments, an alkylene comprises one to four carbon atoms (e.g., C₁-C₄ alkylene). In other embodiments, an alkylene comprises one to three carbon atoms (e.g., C₁-C₃ alkylene). In other embodiments, an alkylene comprises one to two carbon atoms (e.g., C₁-C₂ alkylene). In other embodiments, an alkylene comprises one carbon atom (e.g., C₁

alkylene). In other embodiments, an alkylene comprises two carbon atoms (*e.g.*, C₂ alkylene). In other embodiments, an alkylene comprises two to four carbon atoms (*e.g.*, C₂-C₄ alkylene). Typical alkylene groups include, but are not limited to, -CH₂-, -CH(CH₃)-, -C(CH₃)₂-, -CH₂CH₂-, -CH₂CH(CH₃)-, -CH₂C(CH₃)₂-, -CH₂CH₂CH₂-, -CH₂CH₂CH₂CH₂-, and the like.

[0022] “Deuteroalkyl” refers to an alkyl group where 1 or more hydrogen atoms of an alkyl are replaced with deuterium.

[0023] The term “alkenyl” refers to a type of alkyl group in which at least one carbon-carbon double bond is present. In one embodiment, an alkenyl group has the formula -C(R)=CR₂, wherein R refers to the remaining portions of the alkenyl group, which may be the same or different. In some embodiments, R is H or an alkyl. In some embodiments, an alkenyl is selected from ethenyl (*i.e.*, vinyl), propenyl (*i.e.*, allyl), butenyl, pentenyl, pentadienyl, and the like. Non-limiting examples of an alkenyl group include -CH=CH₂, -C(CH₃)=CH₂, -CH=CHCH₃, -C(CH₃)=CHCH₃, and -CH₂CH=CH₂.

[0024] The term “alkynyl” refers to a type of alkyl group in which at least one carbon-carbon triple bond is present. In one embodiment, an alkynyl group has the formula -C≡C-R, wherein R refers to the remaining portions of the alkynyl group. In some embodiments, R is H or an alkyl. In some embodiments, an alkynyl is selected from ethynyl, propynyl, butynyl, pentynyl, hexynyl, and the like. Non-limiting examples of an alkynyl group include -C≡CH, -C≡CCH₃, -C≡CCH₂CH₃, -CH₂C≡CH.

[0025] An “alkoxy” group refers to a (alkyl)O- group, where alkyl is as defined herein.

[0026] The term “alkylamine” refers to the -N(alkyl)_xH_y group, where x is 0 and y is 2, or where x is 1 and y is 1, or where x is 2 and y is 0.

[0027] The term “aromatic” refers to a planar ring having a delocalized π -electron system containing $4n+2$ π electrons, where n is an integer. The term “aromatic” includes both carbocyclic aryl (“aryl”, *e.g.*, phenyl) and heterocyclic aryl (or “heteroaryl” or “heteroaromatic”) groups (*e.g.*, pyridine). The term includes monocyclic or fused-ring polycyclic (*i.e.*, rings which share adjacent pairs of carbon or nitrogen atoms) groups.

[0028] The term “carbocyclic” or “carbocycle” refers to a ring or ring system where the atoms forming the backbone of the ring are all carbon atoms. The term thus distinguishes carbocyclic from “heterocyclic” rings or “heterocycles” in which the ring backbone contains at least one atom which is different from carbon. In some embodiments, at least one of the two rings of a bicyclic carbocycle is aromatic. In some embodiments, both rings of a bicyclic carbocycle are aromatic. Carbocycle includes cycloalkyl and aryl.

[0029] As used herein, the term “aryl” refers to an aromatic ring wherein each of the atoms forming the ring is a carbon atom. In one aspect, aryl is phenyl or a naphthyl. In some embodiments, an aryl is a phenyl. In some embodiments, an aryl is a C₆-C₁₀aryl. Depending on the structure, an aryl group is a monoradical or a diradical (i.e., an arylene group).

[0030] The term “cycloalkyl” refers to a monocyclic or polycyclic aliphatic, non-aromatic radical, wherein each of the atoms forming the ring (i.e. skeletal atoms) is a carbon atom. In some embodiments, cycloalkyls are spirocyclic or bridged compounds. In some embodiments, cycloalkyls are optionally fused with an aromatic ring, and the point of attachment is at a carbon that is not an aromatic ring carbon atom. Cycloalkyl groups include groups having from 3 to 10 ring atoms. In some embodiments, cycloalkyl groups are selected from among cyclopropyl, cyclobutyl, cyclopentyl, cyclopentenyl, cyclohexyl, cyclohexenyl, cycloheptyl, cyclooctyl, spiro[2.2]pentyl, norbornyl and bicyclo[1.1.1]pentyl. In some embodiments, a cycloalkyl is a C₃-C₆cycloalkyl. In some embodiments, a cycloalkyl is a monocyclic cycloalkyl. Monocyclic cycloalkyls include, but are not limited to, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, and cyclooctyl. Polycyclic cycloalkyls include, for example, adamantyl, norbornyl (i.e., bicyclo[2.2.2]octyl and bicyclo[2.2.1]heptanyl), norbornenyl, decalynyl, 7,7-dimethyl-bicyclo[2.2.1]heptanyl, and the like.

[0031] The term “halo” or, alternatively, “halogen” or “halide” means fluoro, chloro, bromo or iodo. In some embodiments, halo is fluoro, chloro, or bromo.

[0032] The term “haloalkyl” refers to an alkyl in which one or more hydrogen atoms are replaced by a halogen atom. In one aspect, a fluoroalkyl is a C₁-C₆fluoroalkyl.

[0033] The term “fluoroalkyl” refers to an alkyl in which one or more hydrogen atoms are replaced by a fluorine atom. In one aspect, a fluoroalkyl is a C₁-C₆fluoroalkyl. In some embodiments, a fluoroalkyl is selected from trifluoromethyl, difluoromethyl, fluoromethyl, 2,2,2-trifluoroethyl, 1-fluoromethyl-2-fluoroethyl, and the like.

[0034] The term “heteroalkyl” refers to an alkyl group in which one or more skeletal atoms of the alkyl are selected from an atom other than carbon, e.g., oxygen, nitrogen (e.g. -NH-, -N(alkyl)-, sulfur, or combinations thereof. A heteroalkyl is attached to the rest of the molecule at a carbon atom of the heteroalkyl. In one aspect, a heteroalkyl is a C₁-C₆heteroalkyl.

[0035] The term “heteroalkylene” refers to a divalent heteroalkyl radical.

[0036] The term “heterocycle” or “heterocyclic” refers to heteroaromatic rings (also known as heteroaryls) and heterocycloalkyl rings (also known as heteroalicyclic groups) containing one to four heteroatoms in the ring(s), where each heteroatom in the ring(s) is selected from O, S and N, wherein each heterocyclic group has from 3 to 10 atoms in its ring system, and with the proviso

that any ring does not contain two adjacent O or S atoms. In some embodiments, heterocycles are monocyclic, bicyclic, polycyclic, spirocyclic or bridged compounds. Non-aromatic heterocyclic groups (also known as heterocycloalkyls) include rings having 3 to 10 atoms in its ring system and aromatic heterocyclic groups include rings having 5 to 10 atoms in its ring system. The heterocyclic groups include benzo-fused ring systems. Examples of non-aromatic heterocyclic groups are pyrrolidinyl, tetrahydrofuranyl, dihydrofuranyl, tetrahydrothienyl, oxazolidinonyl, tetrahydropyranyl, dihydropyranyl, tetrahydrothiopyranyl, piperidinyl, morpholinyl, thiomorpholinyl, thioxanyl, piperazinyl, aziridinyl, azetidiny, oxetanyl, thietanyl, homopiperidinyl, oxepanyl, thiepanyl, oxazepinyl, diazepinyl, thiazepinyl, 1,2,3,6-tetrahydropyridinyl, pyrrolin-2-yl, pyrrolin-3-yl, indolinyl, 2H-pyranyl, 4H-pyranyl, dioxanyl, 1,3-dioxolanyl, pyrazolinyl, dithianyl, dithiolanyl, dihydropyranyl, dihydrothienyl, dihydrofuranyl, pyrazolidinyl, imidazoliny, imidazolidinyl, 3-azabicyclo[3.1.0]hexanyl, 3-azabicyclo[4.1.0]heptanyl, 2-azabicyclo[2.2.2]octanyl, 3-azabicyclo[3.2.1]octanyl, 5-azabicyclo[2.1.1]hexanyl, 6-azabicyclo[3.1.1]heptanyl, 7-azabicyclo[2.2.1]heptanyl, 8-azabicyclo[3.2.1]octanyl, 3H-indolyl, indolin-2-onyl, isoindolin-1-onyl, isoindoline-1,3-dionyl, 3,4-dihydroisoquinolin-1(2H)-onyl, 3,4-dihydroquinolin-2(1H)-onyl, isoindoline-1,3-dithionyl, benzo[d]oxazol-2(3H)-onyl, 1H-benzo[d]imidazol-2(3H)-onyl, benzo[d]thiazol-2(3H)-onyl, and quinoliziny. Examples of aromatic heterocyclic groups are pyridinyl, imidazolyl, pyrimidinyl, pyrazolyl, triazolyl, pyrazinyl, tetrazolyl, furyl, thienyl, isoxazolyl, thiazolyl, oxazolyl, isothiazolyl, pyrrolyl, quinolinyl, isoquinolinyl, indolyl, benzimidazolyl, benzofuranyl, cinnolinyl, indazolyl, indoliziny, phthalazinyl, pyridazinyl, triazinyl, isoindolyl, pteridinyl, purinyl, oxadiazolyl, thiadiazolyl, furazanyl, benzofurazanyl, benzothiophenyl, benzothiazolyl, benzoxazolyl, quinazolinyl, quinoxaliny, naphthyridinyl, and furopyridinyl. The foregoing groups are either C-attached (or C-linked) or *N*-attached where such is possible. For instance, a group derived from pyrrole includes both pyrrol-1-yl (*N*-attached) or pyrrol-3-yl (C-attached). Further, a group derived from imidazole includes imidazol-1-yl or imidazol-3-yl (both *N*-attached) or imidazol-2-yl, imidazol-4-yl or imidazol-5-yl (all C-attached). The heterocyclic groups include benzo-fused ring systems. Non-aromatic heterocycles are optionally substituted with one or two oxo (=O) moieties, such as pyrrolidin-2-one. In some embodiments, at least one of the two rings of a bicyclic heterocycle is aromatic. In some embodiments, both rings of a bicyclic heterocycle are aromatic.

[0037] The terms “heteroaryl” or, alternatively, “heteroaromatic” refers to an aryl group that includes one or more ring heteroatoms selected from nitrogen, oxygen and sulfur. Illustrative examples of heteroaryl groups include monocyclic heteroaryls and bicyclic heteroaryls.

Monocyclic heteroaryls include pyridinyl, imidazolyl, pyrimidinyl, pyrazolyl, triazolyl, pyrazinyl, tetrazolyl, furyl, thienyl, isoxazolyl, thiazolyl, oxazolyl, isothiazolyl, pyrrolyl, pyridazinyl, triazinyl, oxadiazolyl, thiadiazolyl, and furazanyl. Bicyclic heteroaryls include indolizine, indole, benzofuran, benzothiophene, indazole, benzimidazole, purine, quinolizine, quinoline, isoquinoline, cinnoline, phthalazine, quinazoline, quinoxaline, 1,8-naphthyridine, and pteridine. In some embodiments, a heteroaryl contains 0-4 N atoms in the ring. In some embodiments, a heteroaryl contains 1-4 N atoms in the ring. In some embodiments, a heteroaryl contains 0-4 N atoms, 0-1 O atoms, and 0-1 S atoms in the ring. In some embodiments, a heteroaryl contains 1-4 N atoms, 0-1 O atoms, and 0-1 S atoms in the ring. In some embodiments, heteroaryl is a C₁-C₉heteroaryl. In some embodiments, monocyclic heteroaryl is a C₁-C₃heteroaryl. In some embodiments, monocyclic heteroaryl is a 5-membered or 6-membered heteroaryl. In some embodiments, bicyclic heteroaryl is a C₆-C₉heteroaryl.

[0038] A “heterocycloalkyl” or “heteroalicyclic” group refers to a cycloalkyl group that includes at least one heteroatom selected from nitrogen, oxygen and sulfur. In some embodiments, a heterocycloalkyl is fused with an aryl or heteroaryl. In some embodiments, the heterocycloalkyl is oxazolidinonyl, pyrrolidinyl, tetrahydrofuranyl, tetrahydrothienyl, tetrahydropyranyl, tetrahydrothiopyranyl, piperidinyl, morpholinyl, thiomorpholinyl, piperazinyl, piperidin-2-onyl, pyrrolidine-2,5-dithionyl, pyrrolidine-2,5-dionyl, pyrrolidinonyl, imidazolidinyl, imidazolidin-2-onyl, or thiazolidin-2-onyl. The term heteroalicyclic also includes all ring forms of the carbohydrates, including but not limited to the monosaccharides, the disaccharides and the oligosaccharides. In one aspect, a heterocycloalkyl is a C₂-C₁₀heterocycloalkyl. In another aspect, a heterocycloalkyl is a C₄-C₁₀heterocycloalkyl. In some embodiments, a heterocycloalkyl contains 0-2 N atoms in the ring. In some embodiments, a heterocycloalkyl contains 0-2 N atoms, 0-2 O atoms and 0-1 S atoms in the ring.

[0039] The term “oxo” refers to the =O radical.

[0040] The term “bond” or “single bond” refers to a chemical bond between two atoms, or two moieties when the atoms joined by the bond are considered to be part of larger substructure. In one aspect, when a group described herein is a bond, the referenced group is absent thereby allowing a bond to be formed between the remaining identified groups.

[0041] The term “moiety” refers to a specific segment or functional group of a molecule. Chemical moieties are often recognized chemical entities embedded in or appended to a molecule.

[0042] The term “optionally substituted” or “substituted” means that the referenced group is optionally substituted with one or more additional group(s) individually and independently

selected from D, halogen, -CN, -NH₂, -NH(alkyl), -N(alkyl)₂, -OH, -CO₂H, -CO₂alkyl, -C(=O)NH₂, -C(=O)NH(alkyl), -C(=O)N(alkyl)₂, -S(=O)₂NH₂, -S(=O)₂NH(alkyl), -S(=O)₂N(alkyl)₂, alkyl, alkenyl, alkynyl, cycloalkyl, fluoroalkyl, heteroalkyl, alkoxy, fluoroalkoxy, heterocycloalkyl, aryl, heteroaryl, aryloxy, alkylthio, arylthio, alkylsulfoxide, arylsulfoxide, alkylsulfone, and arylsulfone. In some other embodiments, optional substituents are independently selected from D, halogen, -CN, -NH₂, -NH(CH₃), -N(CH₃)₂, -OH, -CO₂H, -CO₂(C₁-C₄alkyl), -C(=O)NH₂, -C(=O)NH(C₁-C₄alkyl), -C(=O)N(C₁-C₄alkyl)₂, -S(=O)₂NH₂, -S(=O)₂NH(C₁-C₄alkyl), -S(=O)₂N(C₁-C₄alkyl)₂, C₁-C₄alkyl, C₃-C₆cycloalkyl, C₁-C₄fluoroalkyl, C₁-C₄heteroalkyl, C₁-C₄alkoxy, C₁-C₄fluoroalkoxy, -SC₁-C₄alkyl, -S(=O)C₁-C₄alkyl, and -S(=O)₂C₁-C₄alkyl. In some embodiments, optional substituents are independently selected from D, halogen, -CN, -NH₂, -OH, -NH(CH₃), -N(CH₃)₂, -CH₃, -CH₂CH₃, -CF₃, -OCH₃, and -OCF₃. In some embodiments, substituted groups are substituted with one or two of the preceding groups. In some embodiments, an optional substituent on an aliphatic carbon atom (acyclic or cyclic) includes oxo (=O).

[0043] The term “acceptable” with respect to a formulation, composition or ingredient, as used herein, means having no persistent detrimental effect on the general health of the subject being treated.

[0044] The term “modulate” as used herein, means to interact with a target either directly or indirectly so as to alter the activity of the target, including, by way of example only, to enhance the activity of the target, to inhibit the activity of the target, to limit the activity of the target, or to extend the activity of the target.

[0045] The term “modulator” as used herein, refers to a molecule that interacts with a target either directly or indirectly. The interactions include, but are not limited to, the interactions of a corrector, an agonist, partial agonist, an inverse agonist, antagonist, degrader, or combinations thereof. In some embodiments, a modulator is a corrector.

[0046] The terms “administer,” “administering,” “administration,” and the like, as used herein, refer to the methods that may be used to enable delivery of compounds or compositions to the desired site of biological action. These methods include, but are not limited to oral routes, intraduodenal routes, parenteral injection (including intravenous, subcutaneous, intraperitoneal, intramuscular, intravascular or infusion), topical and rectal administration. Those of skill in the art are familiar with administration techniques that can be employed with the compounds and methods described herein. In some embodiments, the compounds and compositions described herein are administered orally.

[0047] The terms “co-administration” or the like, as used herein, are meant to encompass administration of the selected therapeutic agents to a single patient and are intended to include treatment regimens in which the agents are administered by the same or different route of administration or at the same or different time.

[0048] The terms “effective amount” or “therapeutically effective amount,” as used herein, refer to a sufficient amount of an agent or a compound being administered, which will relieve to some extent one or more of the symptoms of the disease or condition being treated. The result includes reduction and/or alleviation of the signs, symptoms, or causes of a disease, or any other desired alteration of a biological system. For example, an “effective amount” for therapeutic uses is the amount of the composition comprising a compound as disclosed herein required to provide a clinically significant decrease in disease symptoms. An appropriate “effective” amount in any individual case is optionally determined using techniques, such as a dose escalation study.

[0049] The terms “enhance” or “enhancing,” as used herein, means to increase or prolong either in potency or duration a desired effect. Thus, in regard to enhancing the effect of therapeutic agents, the term “enhancing” refers to the ability to increase or prolong, either in potency or duration, the effect of other therapeutic agents on a system. An “enhancing-effective amount,” as used herein, refers to an amount adequate to enhance the effect of another therapeutic agent in a desired system.

[0050] The terms “kit” and “article of manufacture” are used as synonyms.

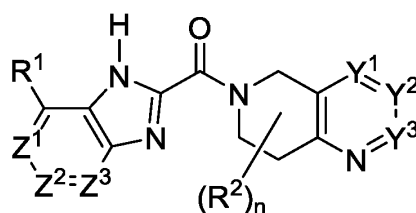
[0051] The term “subject” or “patient” encompasses mammals. Examples of mammals include, but are not limited to, any member of the Mammalian class: humans, non-human primates such as chimpanzees, and other apes and monkey species; farm animals such as cattle, horses, sheep, goats, swine; domestic animals such as rabbits, dogs, and cats; laboratory animals including rodents, such as rats, mice and guinea pigs, and the like. In one aspect, the mammal is a human.

[0052] The terms “treat,” “treating” or “treatment,” as used herein, include alleviating, abating or ameliorating at least one symptom of a disease or condition, preventing additional symptoms, inhibiting the disease or condition, e.g., arresting the development of the disease or condition, relieving the disease or condition, causing regression of the disease or condition, relieving a condition caused by the disease or condition, or stopping the symptoms of the disease or condition either prophylactically and/or therapeutically.

Compounds

[0053] Compounds described herein, including pharmaceutically acceptable salts, active metabolites and pharmaceutically acceptable solvates thereof, are small molecule correctors of rhodopsin.

[0054] In some embodiments, described herein is a compound of Formula (I), or a pharmaceutically acceptable salt or solvate thereof:



Formula (I);

wherein,

Y¹, Y², and Y³ are each independently C(R³) or N, wherein at least one of Y² and Y³ is C(R³);

Z¹, Z², and Z³ are each independently C(R⁴) or N, wherein at least one of Z¹, Z², and Z³ is C(R⁴);

R¹ is selected from hydrogen, halogen, -CN, -OR¹⁰, -SR¹⁰, -N(R¹⁰)(R¹¹), -C(O)OR¹⁰, -OC(O)N(R¹⁰)(R¹¹), -N(R¹²)C(O)N(R¹⁰)(R¹¹), -N(R¹²)C(O)OR¹³, -N(R¹²)S(O)₂R¹³, -C(O)R¹³, -S(O)R¹³, -OC(O)R¹³, -C(O)N(R¹⁰)(R¹¹), -N(R¹²)C(O)R¹³, -S(O)₂R¹³, -S(O)₂N(R¹⁰)(R¹¹), -S(=O)(=NH)N(R¹⁰)(R¹¹), C₁₋₆alkyl, C₁₋₆haloalkyl, C₂₋₆alkenyl, C₂₋₆alkynyl, C₃₋₆cycloalkyl, C₂₋₉heterocycloalkyl, C₆₋₁₀aryl, and C₁₋₉heteroaryl, wherein C₁₋₆alkyl, C₁₋₆haloalkyl, C₂₋₆alkenyl, C₂₋₆alkynyl, C₃₋₆cycloalkyl, C₂₋₉heterocycloalkyl, C₆₋₁₀aryl, and C₁₋₉heteroaryl are optionally substituted with 1-5 R^{5a} groups;

each R² is independently selected from halogen, -CN, -OR¹⁰, -SR¹⁰, -N(R¹⁰)(R¹¹), C₁₋₆alkyl, C₁₋₆haloalkyl, C₂₋₆alkenyl, C₂₋₆alkynyl, C₃₋₆cycloalkyl, C₂₋₉heterocycloalkyl, C₆₋₁₀aryl, and C₁₋₉heteroaryl, wherein C₁₋₆alkyl, C₁₋₆haloalkyl, C₂₋₆alkenyl, C₂₋₆alkynyl, C₃₋₆cycloalkyl, C₂₋₉heterocycloalkyl, C₆₋₁₀aryl, and C₁₋₉heteroaryl are optionally substituted with 1-5 R^{5b} groups;

each R³ is independently selected from hydrogen, halogen, -CN, -SR¹⁰, -N(R¹⁰)(R¹¹), C₁₋₆alkyl, C₁₋₆haloalkyl, C₁₋₆alkoxy, C₂₋₆alkenyl, C₂₋₆alkynyl, C₃₋₆cycloalkyl, C₂₋₉heterocycloalkyl, C₆₋₁₀aryl, and C₁₋₉heteroaryl, wherein C₁₋₆alkyl, C₁₋₆haloalkyl, C₁₋₆alkoxy, C₂₋₆alkenyl, C₂₋₆alkynyl, C₃₋₆cycloalkyl, C₂₋₉heterocycloalkyl, C₆₋₁₀aryl, and C₁₋₉heteroaryl are optionally substituted with 1-5 R^{5c} groups;

each R⁴ is independently selected from hydrogen, halogen, -CN, -OR¹⁰, -SR¹⁰, -N(R¹⁰)(R¹¹), C₁₋₆alkyl, C₁₋₆haloalkyl, C₂₋₆alkenyl, C₂₋₆alkynyl, C₃₋₆cycloalkyl, C₂₋₉heterocycloalkyl, C₆₋₁₀aryl, and C₁₋₉heteroaryl, wherein C₁₋₆alkyl, C₁₋₆haloalkyl, C₂₋₆alkenyl, C₂₋₆alkynyl,

C₃₋₆cycloalkyl, C₂₋₉heterocycloalkyl, C₆₋₁₀aryl, and C₁₋₉heteroaryl are optionally substituted with 1-5 R^{5d} groups;

each R^{5a}, R^{5b}, R^{5c}, and R^{5d} is each independently selected from halogen, oxo, -CN, C₁₋₆alkyl, C₁₋₆haloalkyl, C₂₋₆alkenyl, C₂₋₆alkynyl, C₃₋₆cycloalkyl, -CH₂-C₃₋₆cycloalkyl, C₂₋₉heterocycloalkyl, -CH₂-C₂₋₉heterocycloalkyl, C₆₋₁₀aryl, -CH₂-C₆₋₁₀aryl, C₁₋₉heteroaryl, -CH₂-C₁₋₉heteroaryl, -OR¹⁰, -SR¹⁰, -N(R¹⁰)(R¹¹), -C(O)OR¹⁰, -OC(O)N(R¹⁰)(R¹¹), -N(R¹²)C(O)N(R¹⁰)(R¹¹), -N(R¹²)C(O)OR¹³, -N(R¹²)S(O)₂R¹³, -C(O)R¹³, -S(O)R¹³, -OC(O)R¹³, -C(O)N(R¹⁰)(R¹¹), -C(O)C(O)N(R¹⁰)(R¹¹), -N(R¹²)C(O)R¹³, -S(O)₂R¹³, -S(O)₂N(R¹⁰)(R¹¹), -S(=O)(=NH)N(R¹⁰)(R¹¹), -C(=NOR¹¹)R¹³, -CH₂C(O)N(R¹⁰)(R¹¹), -CH₂N(R¹²)C(O)R¹³, -CH₂S(O)₂R¹³, and -CH₂S(O)₂N(R¹⁰)(R¹¹), wherein C₁₋₆alkyl, C₁₋₆haloalkyl, C₂₋₆alkenyl, C₂₋₆alkynyl, C₃₋₆cycloalkyl, -CH₂-C₃₋₆cycloalkyl, C₂₋₉heterocycloalkyl, -CH₂-C₂₋₉heterocycloalkyl, C₆₋₁₀aryl, -CH₂-C₆₋₁₀aryl, C₁₋₉heteroaryl, -CH₂-C₁₋₉heteroaryl are optionally substituted with one, two, or three groups selected from halogen, -CN, C₁₋₆alkyl, C₁₋₆haloalkyl, C₃₋₆cycloalkyl, C₂₋₉heterocycloalkyl, C₆₋₁₀aryl, C₁₋₉heteroaryl, -OR¹⁰, and -N(R¹⁰)(R¹¹);

each R¹⁰ is independently selected from hydrogen, C₁₋₆alkyl, C₁₋₆haloalkyl, C₂₋₆alkenyl, C₂₋₆alkynyl, C₃₋₆cycloalkyl, C₂₋₉heterocycloalkyl, C₆₋₁₀aryl, and C₁₋₉heteroaryl, wherein C₁₋₆alkyl, C₂₋₆alkenyl, C₂₋₆alkynyl, C₃₋₆cycloalkyl, C₂₋₉heterocycloalkyl, C₆₋₁₀aryl, and C₁₋₉heteroaryl are optionally substituted with one, two, or three groups selected from halogen, -CN, hydroxy, C₁₋₆alkyl, C₁₋₆haloalkyl, C₁₋₆alkoxy, C₃₋₆cycloalkyl, C₂₋₉heterocycloalkyl, C₆₋₁₀aryl, and C₁₋₉heteroaryl;

each R¹¹ is independently selected from hydrogen, C₁₋₆alkyl, and C₁₋₆haloalkyl;

each R¹² is independently selected from hydrogen, C₁₋₆alkyl, and C₁₋₆haloalkyl;

each R¹³ is independently selected C₁₋₆alkyl, C₂₋₆alkenyl, C₂₋₆alkynyl, C₃₋₆cycloalkyl, C₂₋₉heterocycloalkyl, C₆₋₁₀aryl, and C₁₋₉heteroaryl, wherein C₁₋₆alkyl, C₂₋₆alkenyl, C₂₋₆alkynyl, C₃₋₆cycloalkyl, C₂₋₉heterocycloalkyl, C₆₋₁₀aryl, and C₁₋₉heteroaryl are optionally substituted with one, two, or three groups selected from halogen, -CN, hydroxy, C₁₋₆alkyl, C₁₋₆haloalkyl, C₁₋₆alkoxy, C₃₋₆cycloalkyl, C₂₋₉heterocycloalkyl, C₆₋₁₀aryl, and C₁₋₉heteroaryl; and

n is 0, 1, 2, 3, or 4.

[0055] In some embodiments is a compound of Formula (I), or a pharmaceutically acceptable salt or solvate thereof, wherein Y¹, Y², and Y³ are each C(R³). In some embodiments is a compound of Formula (I), or a pharmaceutically acceptable salt or solvate thereof, wherein Y¹ and Y³ are C(R³) and Y² is N. In some embodiments is a compound of Formula (I), or a

pharmaceutically acceptable salt or solvate thereof, wherein Y^1 and Y^2 are $C(R^3)$ and Y^3 is N. In some embodiments is a compound of Formula (I), or a pharmaceutically acceptable salt or solvate thereof, wherein Y^2 and Y^3 are $C(R^3)$ and Y^1 is N.

[0056] In some embodiments is a compound of Formula (I), or a pharmaceutically acceptable salt or solvate thereof, wherein each R^3 is independently selected from hydrogen, halogen, -CN, - $N(R^{10})(R^{11})$, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} alkoxy, and C_{3-6} cycloalkyl, wherein C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} alkoxy, and C_{3-6} cycloalkyl are optionally substituted with 1-5 R^{5c} groups. In some embodiments is a compound of Formula (I), or a pharmaceutically acceptable salt or solvate thereof, wherein each R^3 is independently selected from hydrogen, halogen, -CN, C_{1-6} alkyl, C_{1-6} haloalkyl, and C_{1-6} alkoxy, wherein C_{1-6} alkyl, C_{1-6} haloalkyl, and C_{1-6} alkoxy are optionally substituted with 1-5 R^{5c} groups. In some embodiments is a compound of Formula (I), or a pharmaceutically acceptable salt or solvate thereof, wherein each R^3 is independently selected from hydrogen, halogen, -CN, C_{1-6} alkyl, C_{1-6} haloalkyl, and C_{1-6} alkoxy, wherein C_{1-6} alkyl, C_{1-6} haloalkyl, and C_{1-6} alkoxy are optionally substituted with 1-3 R^{5c} groups. In some embodiments is a compound of Formula (I), or a pharmaceutically acceptable salt or solvate thereof, wherein each R^3 is independently selected from hydrogen, halogen, -CN, unsubstituted C_{1-6} alkyl, -CF₃, and -OCH₃. In some embodiments is a compound of Formula (I), or a pharmaceutically acceptable salt or solvate thereof, wherein each R^3 is independently selected from hydrogen, halogen, and -CH₃. In some embodiments is a compound of Formula (I), or a pharmaceutically acceptable salt or solvate thereof, wherein each R^3 is hydrogen.

[0057] In some embodiments is a compound of Formula (I), or a pharmaceutically acceptable salt or solvate thereof, wherein each R^2 is independently selected from -OR¹⁰, C_{1-6} alkyl, and C_{1-6} haloalkyl, wherein C_{1-6} alkyl and C_{1-6} haloalkyl are optionally substituted with 1-5 R^{5b} groups. In some embodiments is a compound of Formula (I), or a pharmaceutically acceptable salt or solvate thereof, wherein each R^2 is independently selected from C_{1-6} alkyl optionally substituted with 1-5 R^{5b} groups. In some embodiments is a compound of Formula (I), or a pharmaceutically acceptable salt or solvate thereof, wherein each R^2 is independently selected from C_{1-6} alkyl optionally substituted with -OH. In some embodiments is a compound of Formula (I), or a pharmaceutically acceptable salt or solvate thereof, wherein each R^2 is -CH₂OH. In some embodiments is a compound of Formula (I), or a pharmaceutically acceptable salt or solvate thereof, wherein each R^2 is independently selected from unsubstituted C_{1-6} alkyl. In some embodiments is a compound of Formula (I), or a pharmaceutically acceptable salt or solvate thereof, wherein each R^2 is -CH₃. In some embodiments is a compound of Formula (I), or a pharmaceutically acceptable salt or solvate thereof, wherein each R^2 is -CH₂CH₃. In some

embodiments is a compound of Formula (I), or a pharmaceutically acceptable salt or solvate thereof, wherein each R^2 is $-\text{CH}(\text{CH}_3)_2$. In some embodiments is a compound of Formula (I), or a pharmaceutically acceptable salt or solvate thereof, wherein each R^2 is independently selected from $-\text{OR}^{10}$, wherein R^{10} is C_{1-6} alkyl. In some embodiments is a compound of Formula (I), or a pharmaceutically acceptable salt or solvate thereof, wherein each R^2 is $-\text{OCH}_3$.

[0058] In some embodiments is a compound of Formula (I), or a pharmaceutically acceptable salt or solvate thereof, wherein n is 1. In some embodiments is a compound of Formula (I), or a pharmaceutically acceptable salt or solvate thereof, wherein n is 2. In some embodiments is a compound of Formula (I), or a pharmaceutically acceptable salt or solvate thereof, wherein n is 3. In some embodiments is a compound of Formula (I), or a pharmaceutically acceptable salt or solvate thereof, wherein n is 4. In some embodiments is a compound of Formula (I), or a pharmaceutically acceptable salt or solvate thereof, wherein n is 0.

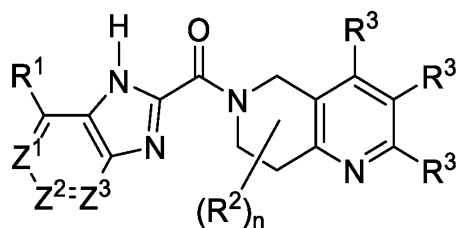
[0059] In some embodiments is a compound of Formula (I), or a pharmaceutically acceptable salt or solvate thereof, wherein R^1 is selected from halogen, $-\text{CN}$, $-\text{OR}^{10}$, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{6-10} aryl, and C_{1-9} heteroaryl, wherein C_{1-6} alkyl and C_{1-6} haloalkyl are optionally substituted with 1-5 R^{5a} groups. In some embodiments is a compound of Formula (I), or a pharmaceutically acceptable salt or solvate thereof, wherein R^1 is selected from halogen, $-\text{CN}$, $-\text{OR}^{10}$, C_{1-6} alkyl, and C_{1-6} haloalkyl wherein C_{1-6} alkyl and C_{1-6} haloalkyl are optionally substituted with 1-5 R^{5a} groups. In some embodiments is a compound of Formula (I), or a pharmaceutically acceptable salt or solvate thereof, wherein R^1 is selected from halogen, $-\text{CN}$, $-\text{OR}^{10}$, unsubstituted C_{1-6} alkyl, and unsubstituted C_{1-6} haloalkyl. In some embodiments is a compound of Formula (I), or a pharmaceutically acceptable salt or solvate thereof, wherein R^1 is halogen. In some embodiments is a compound of Formula (I), or a pharmaceutically acceptable salt or solvate thereof, wherein R^1 is $-\text{CN}$. In some embodiments is a compound of Formula (I), or a pharmaceutically acceptable salt or solvate thereof, wherein R^1 is $-\text{OR}^{10}$. In some embodiments is a compound of Formula (I), or a pharmaceutically acceptable salt or solvate thereof, wherein R^1 is $-\text{OR}^{10}$, wherein R^{10} is hydrogen C_{1-6} alkyl. In some embodiments is a compound of Formula (I), or a pharmaceutically acceptable salt or solvate thereof, wherein R^1 is $-\text{OH}$. In some embodiments is a compound of Formula (I), or a pharmaceutically acceptable salt or solvate thereof, wherein R^1 is $-\text{OCH}_3$. In some embodiments is a compound of Formula (I), or a pharmaceutically acceptable salt or solvate thereof, wherein R^1 is unsubstituted C_{1-6} alkyl. In some embodiments is a compound of Formula (I), or a pharmaceutically acceptable salt or solvate thereof, wherein R^1 is $-\text{CH}_3$. In some embodiments is a compound of Formula (I), or a pharmaceutically acceptable salt or solvate thereof, wherein R^1 is unsubstituted C_{1-6} haloalkyl. In some embodiments is a compound

of Formula (I), or a pharmaceutically acceptable salt or solvate thereof, wherein R^1 is $-CF_3$. In some embodiments is a compound of Formula (I), or a pharmaceutically acceptable salt or solvate thereof, wherein R^1 is selected from halogen, $-CN$, $-OH$, $-OCH_3$, $-CH_3$, and $-CF_3$.

[0060] In some embodiments is a compound of Formula (I), or a pharmaceutically acceptable salt or solvate thereof, wherein Z^1 , Z^2 , and Z^3 are each independently $C(R^4)$. In some embodiments is a compound of Formula (I), or a pharmaceutically acceptable salt or solvate thereof, wherein Z^1 and Z^2 are $C(R^4)$ and Z^3 is N. In some embodiments is a compound of Formula (I), or a pharmaceutically acceptable salt or solvate thereof, wherein Z^1 and Z^3 are N and Z^2 is $C(R^4)$. In some embodiments is a compound of Formula (I), or a pharmaceutically acceptable salt or solvate thereof, wherein Z^1 and Z^3 are $C(R^4)$ and Z^2 is N. In some embodiments is a compound of Formula (I), or a pharmaceutically acceptable salt or solvate thereof, wherein Z^2 and Z^3 are $C(R^4)$ and Z^1 is N.

[0061] In some embodiments is a compound of Formula (I), or a pharmaceutically acceptable salt or solvate thereof, wherein each R^4 is independently selected from hydrogen, halogen, $-CN$, $-OR^{10}$, $C_{1-6}alkyl$, $C_{1-6}haloalkyl$, and $C_{3-6}cycloalkyl$, wherein $C_{1-6}alkyl$, $C_{1-6}haloalkyl$, and $C_{3-6}cycloalkyl$ are optionally substituted with 1-5 R^{5d} groups. In some embodiments is a compound of Formula (I), or a pharmaceutically acceptable salt or solvate thereof, wherein each R^4 is independently selected from hydrogen, halogen, and unsubstituted $C_{1-6}alkyl$. In some embodiments is a compound of Formula (I), or a pharmaceutically acceptable salt or solvate thereof, wherein each R^4 is independently selected from hydrogen and halogen. In some embodiments is a compound of Formula (I), or a pharmaceutically acceptable salt or solvate thereof, wherein each R^4 is hydrogen.

[0062] In some embodiments, described herein is a compound of Formula (Ia), or a pharmaceutically acceptable salt or solvate thereof:



Formula (Ia);

wherein,

Z^1 , Z^2 , and Z^3 are each independently $C(R^4)$ or N, wherein at least one of Z^1 , Z^2 , and Z^3 is $C(R^4)$;

R^1 is selected from hydrogen, halogen, -CN, -OR¹⁰, -SR¹⁰, -N(R¹⁰)(R¹¹), -C(O)OR¹⁰, -OC(O)N(R¹⁰)(R¹¹), -N(R¹²)C(O)N(R¹⁰)(R¹¹), -N(R¹²)C(O)OR¹³, -N(R¹²)S(O)₂R¹³, -C(O)R¹³, -S(O)R¹³, -OC(O)R¹³, -C(O)N(R¹⁰)(R¹¹), -N(R¹²)C(O)R¹³, -S(O)₂R¹³, -S(O)₂N(R¹⁰)(R¹¹), -S(=O)(=NH)N(R¹⁰)(R¹¹), C₁₋₆alkyl, C₁₋₆haloalkyl, C₂₋₆alkenyl, C₂₋₆alkynyl, C₃₋₆cycloalkyl, C₂₋₉heterocycloalkyl, C₆₋₁₀aryl, and C₁₋₉heteroaryl, wherein C₁₋₆alkyl, C₁₋₆haloalkyl, C₂₋₆alkenyl, C₂₋₆alkynyl, C₃₋₆cycloalkyl, C₂₋₉heterocycloalkyl, C₆₋₁₀aryl, and C₁₋₉heteroaryl are optionally substituted with 1-5 R^{5a} groups;

each R² is independently selected from halogen, -CN, -OR¹⁰, -SR¹⁰, -N(R¹⁰)(R¹¹), C₁₋₆alkyl, C₁₋₆haloalkyl, C₂₋₆alkenyl, C₂₋₆alkynyl, C₃₋₆cycloalkyl, C₂₋₉heterocycloalkyl, C₆₋₁₀aryl, and C₁₋₉heteroaryl, wherein C₁₋₆alkyl, C₁₋₆haloalkyl, C₂₋₆alkenyl, C₂₋₆alkynyl, C₃₋₆cycloalkyl, C₂₋₉heterocycloalkyl, C₆₋₁₀aryl, and C₁₋₉heteroaryl are optionally substituted with 1-5 R^{5b} groups;

each R³ is independently selected from hydrogen, halogen, -CN, -SR¹⁰, -N(R¹⁰)(R¹¹), C₁₋₆alkyl, C₁₋₆haloalkyl, C₁₋₆alkoxy, C₂₋₆alkenyl, C₂₋₆alkynyl, C₃₋₆cycloalkyl, C₂₋₉heterocycloalkyl, C₆₋₁₀aryl, and C₁₋₉heteroaryl, wherein C₁₋₆alkyl, C₁₋₆haloalkyl, C₁₋₆alkoxy, C₂₋₆alkenyl, C₂₋₆alkynyl, C₃₋₆cycloalkyl, C₂₋₉heterocycloalkyl, C₆₋₁₀aryl, and C₁₋₉heteroaryl are optionally substituted with 1-5 R^{5c} groups;

each R⁴ is independently selected from hydrogen, halogen, -CN, -OR¹⁰, -SR¹⁰, -N(R¹⁰)(R¹¹), C₁₋₆alkyl, C₁₋₆haloalkyl, C₂₋₆alkenyl, C₂₋₆alkynyl, C₃₋₆cycloalkyl, C₂₋₉heterocycloalkyl, C₆₋₁₀aryl, and C₁₋₉heteroaryl, wherein C₁₋₆alkyl, C₁₋₆haloalkyl, C₂₋₆alkenyl, C₂₋₆alkynyl, C₃₋₆cycloalkyl, C₂₋₉heterocycloalkyl, C₆₋₁₀aryl, and C₁₋₉heteroaryl are optionally substituted with 1-5 R^{5d} groups;

each R^{5a}, R^{5b}, R^{5c}, and R^{5d} is each independently selected from halogen, oxo, -CN, C₁₋₆alkyl, C₁₋₆haloalkyl, C₂₋₆alkenyl, C₂₋₆alkynyl, C₃₋₆cycloalkyl, -CH₂-C₃₋₆cycloalkyl, C₂₋₉heterocycloalkyl, -CH₂-C₂₋₉heterocycloalkyl, C₆₋₁₀aryl, -CH₂-C₆₋₁₀aryl, C₁₋₉heteroaryl, -CH₂-C₁₋₉heteroaryl, -OR¹⁰, -SR¹⁰, -N(R¹⁰)(R¹¹), -C(O)OR¹⁰, -OC(O)N(R¹⁰)(R¹¹), -N(R¹²)C(O)N(R¹⁰)(R¹¹), -N(R¹²)C(O)OR¹³, -N(R¹²)S(O)₂R¹³, -C(O)R¹³, -S(O)R¹³, -OC(O)R¹³, -C(O)N(R¹⁰)(R¹¹), -C(O)C(O)N(R¹⁰)(R¹¹), -N(R¹²)C(O)R¹³, -S(O)₂R¹³, -S(O)₂N(R¹⁰)(R¹¹), -S(=O)(=NH)N(R¹⁰)(R¹¹), -C(=NOR¹¹)R¹³, -CH₂C(O)N(R¹⁰)(R¹¹), -CH₂N(R¹²)C(O)R¹³, -CH₂S(O)₂R¹³, and -CH₂S(O)₂N(R¹⁰)(R¹¹), wherein C₁₋₆alkyl, C₁₋₆haloalkyl, C₂₋₆alkenyl, C₂₋₆alkynyl, C₃₋₆cycloalkyl, -CH₂-C₃₋₆cycloalkyl, C₂₋₉heterocycloalkyl, -CH₂-C₂₋₉heterocycloalkyl, C₆₋₁₀aryl, -CH₂-C₆₋₁₀aryl, C₁₋₉heteroaryl, -CH₂-C₁₋₉heteroaryl are optionally substituted with one, two, or three groups selected from

halogen, -CN, C₁₋₆alkyl, C₁₋₆haloalkyl, C₃₋₆cycloalkyl, C₂₋₉heterocycloalkyl, C₆₋₁₀aryl, C₁₋₉heteroaryl, -OR¹⁰, and -N(R¹⁰)(R¹¹);

each R¹⁰ is independently selected from hydrogen, C₁₋₆alkyl, C₁₋₆ haloalkyl, C₂₋₆alkenyl, C₂₋₆alkynyl, C₃₋₆cycloalkyl, C₂₋₉heterocycloalkyl, C₆₋₁₀aryl, and C₁₋₉heteroaryl, wherein C₁₋₆alkyl, C₂₋₆alkenyl, C₂₋₆alkynyl, C₃₋₆cycloalkyl, C₂₋₉heterocycloalkyl, C₆₋₁₀aryl, and C₁₋₉heteroaryl are optionally substituted with one, two, or three groups selected from halogen, -CN, hydroxy, C₁₋₆alkyl, C₁₋₆haloalkyl, C₁₋₆alkoxy, C₃₋₆cycloalkyl, C₂₋₉heterocycloalkyl, C₆₋₁₀aryl, and C₁₋₉heteroaryl;

each R¹¹ is independently selected from hydrogen, C₁₋₆alkyl, and C₁₋₆haloalkyl;

each R¹² is independently selected from hydrogen, C₁₋₆alkyl, and C₁₋₆haloalkyl;

each R¹³ is independently selected C₁₋₆alkyl, C₂₋₆alkenyl, C₂₋₆alkynyl, C₃₋₆cycloalkyl, C₂₋₉heterocycloalkyl, C₆₋₁₀aryl, and C₁₋₉heteroaryl, wherein C₁₋₆alkyl, C₂₋₆alkenyl, C₂₋₆alkynyl, C₃₋₆cycloalkyl, C₂₋₉heterocycloalkyl, C₆₋₁₀aryl, and C₁₋₉heteroaryl are optionally substituted with one, two, or three groups selected from halogen, -CN, hydroxy, C₁₋₆alkyl, C₁₋₆haloalkyl, C₁₋₆alkoxy, C₃₋₆cycloalkyl, C₂₋₉heterocycloalkyl, C₆₋₁₀aryl, and C₁₋₉heteroaryl; and

n is 0, 1, 2, 3, or 4.

[0063] In some embodiments is a compound of Formula (Ia), or a pharmaceutically acceptable salt or solvate thereof, wherein each R³ is independently selected from hydrogen, halogen, -CN, -N(R¹⁰)(R¹¹), C₁₋₆alkyl, C₁₋₆haloalkyl, C₁₋₆alkoxy, and C₃₋₆cycloalkyl, wherein C₁₋₆alkyl, C₁₋₆haloalkyl, C₁₋₆alkoxy, and C₃₋₆cycloalkyl are optionally substituted with 1-5 R^{5c} groups. In some embodiments is a compound of Formula (Ia), or a pharmaceutically acceptable salt or solvate thereof, wherein each R³ is independently selected from hydrogen, halogen, -CN, C₁₋₆alkyl, C₁₋₆haloalkyl, and C₁₋₆alkoxy, wherein C₁₋₆alkyl, C₁₋₆haloalkyl, and C₁₋₆alkoxy are optionally substituted with 1-5 R^{5c} groups. In some embodiments is a compound of Formula (Ia), or a pharmaceutically acceptable salt or solvate thereof, wherein each R³ is independently selected from hydrogen, halogen, -CN, C₁₋₆alkyl, C₁₋₆haloalkyl, and C₁₋₆alkoxy, wherein C₁₋₆alkyl, C₁₋₆haloalkyl, and C₁₋₆alkoxy are optionally substituted with 1-3 R^{5c} groups. In some embodiments is a compound of Formula (Ia), or a pharmaceutically acceptable salt or solvate thereof, wherein each R³ is independently selected from hydrogen, halogen, -CN, unsubstituted C₁₋₆alkyl, -CF₃, and -OCH₃. In some embodiments is a compound of Formula (Ia), or a pharmaceutically acceptable salt or solvate thereof, wherein each R³ is independently selected from hydrogen, halogen, and -CH₃. In some embodiments is a compound of Formula (Ia), or a pharmaceutically acceptable salt or solvate thereof, wherein each R³ is hydrogen.

[0064] In some embodiments is a compound of Formula (Ia), or a pharmaceutically acceptable salt or solvate thereof, wherein each R^2 is independently selected from $-OR^{10}$, C_{1-6} alkyl, and C_{1-6} haloalkyl, wherein C_{1-6} alkyl and C_{1-6} haloalkyl are optionally substituted with 1-5 R^{5b} groups. In some embodiments is a compound of Formula (Ia), or a pharmaceutically acceptable salt or solvate thereof, wherein each R^2 is independently selected from C_{1-6} alkyl optionally substituted with 1-5 R^{5b} groups. In some embodiments is a compound of Formula (Ia), or a pharmaceutically acceptable salt or solvate thereof, wherein each R^2 is independently selected from C_{1-6} alkyl optionally substituted with $-OH$. In some embodiments is a compound of Formula (Ia), or a pharmaceutically acceptable salt or solvate thereof, wherein each R^2 is $-CH_2OH$. In some embodiments is a compound of Formula (Ia), or a pharmaceutically acceptable salt or solvate thereof, wherein each R^2 is independently selected from unsubstituted C_{1-6} alkyl. In some embodiments is a compound of Formula (Ia), or a pharmaceutically acceptable salt or solvate thereof, wherein each R^2 is $-CH_3$. In some embodiments is a compound of Formula (Ia), or a pharmaceutically acceptable salt or solvate thereof, wherein each R^2 is $-CH_2CH_3$. In some embodiments is a compound of Formula (Ia), or a pharmaceutically acceptable salt or solvate thereof, wherein each R^2 is $-CH(CH_3)_2$. In some embodiments is a compound of Formula (Ia), or a pharmaceutically acceptable salt or solvate thereof, wherein each R^2 is independently selected from $-OR^{10}$, wherein R^{10} is C_{1-6} alkyl. In some embodiments is a compound of Formula (Ia), or a pharmaceutically acceptable salt or solvate thereof, wherein each R^2 is $-OCH_3$.

[0065] In some embodiments is a compound of Formula (Ia), or a pharmaceutically acceptable salt or solvate thereof, wherein n is 1. In some embodiments is a compound of Formula (Ia), or a pharmaceutically acceptable salt or solvate thereof, wherein n is 2. In some embodiments is a compound of Formula (Ia), or a pharmaceutically acceptable salt or solvate thereof, wherein n is 3. In some embodiments is a compound of Formula (Ia), or a pharmaceutically acceptable salt or solvate thereof, wherein n is 4. In some embodiments is a compound of Formula (Ia), or a pharmaceutically acceptable salt or solvate thereof, wherein n is 0.

[0066] In some embodiments is a compound of Formula (Ia), or a pharmaceutically acceptable salt or solvate thereof, wherein R^1 is selected from halogen, $-CN$, $-OR^{10}$, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{6-10} aryl, and C_{1-9} heteroaryl, wherein C_{1-6} alkyl and C_{1-6} haloalkyl are optionally substituted with 1-5 R^{5a} groups. In some embodiments is a compound of Formula (Ia), or a pharmaceutically acceptable salt or solvate thereof, wherein R^1 is selected from halogen, $-CN$, $-OR^{10}$, C_{1-6} alkyl, and C_{1-6} haloalkyl wherein C_{1-6} alkyl and C_{1-6} haloalkyl are optionally substituted with 1-5 R^{5a} groups. In some embodiments is a compound of Formula (Ia), or a pharmaceutically acceptable salt or solvate thereof, wherein R^1 is selected from halogen, $-CN$, $-OR^{10}$, unsubstituted C_{1-6} alkyl,

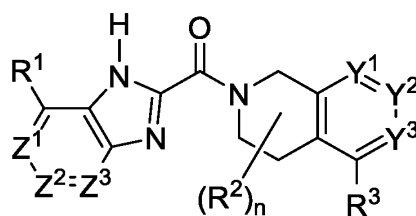
and unsubstituted C₁₋₆haloalkyl. In some embodiments is a compound of Formula (Ia), or a pharmaceutically acceptable salt or solvate thereof, wherein R¹ is halogen. In some embodiments is a compound of Formula (Ia), or a pharmaceutically acceptable salt or solvate thereof, wherein R¹ is -CN. In some embodiments is a compound of Formula (Ia), or a pharmaceutically acceptable salt or solvate thereof, wherein R¹ is -OR¹⁰. In some embodiments is a compound of Formula (Ia), or a pharmaceutically acceptable salt or solvate thereof, wherein R¹ is -OR¹⁰, wherein R¹⁰ is hydrogen C₁₋₆alkyl. In some embodiments is a compound of Formula (Ia), or a pharmaceutically acceptable salt or solvate thereof, wherein R¹ is -OH. In some embodiments is a compound of Formula (Ia), or a pharmaceutically acceptable salt or solvate thereof, wherein R¹ is -OCH₃. In some embodiments is a compound of Formula (Ia), or a pharmaceutically acceptable salt or solvate thereof, wherein R¹ is unsubstituted C₁₋₆alkyl. In some embodiments is a compound of Formula (Ia), or a pharmaceutically acceptable salt or solvate thereof, wherein R¹ is -CH₃. In some embodiments is a compound of Formula (Ia), or a pharmaceutically acceptable salt or solvate thereof, wherein R¹ is unsubstituted C₁₋₆haloalkyl. In some embodiments is a compound of Formula (Ia), or a pharmaceutically acceptable salt or solvate thereof, wherein R¹ is -CF₃. In some embodiments is a compound of Formula (Ia), or a pharmaceutically acceptable salt or solvate thereof, wherein R¹ is selected from halogen, -CN, -OH, -OCH₃, -CH₃, and -CF₃.

[0067] In some embodiments is a compound of Formula (Ia), or a pharmaceutically acceptable salt or solvate thereof, wherein Z¹, Z², and Z³ are each independently C(R⁴). In some embodiments is a compound of Formula (Ia), or a pharmaceutically acceptable salt or solvate thereof, wherein Z¹ and Z² are C(R⁴) and Z³ is N. In some embodiments is a compound of Formula (Ia), or a pharmaceutically acceptable salt or solvate thereof, wherein Z¹ and Z³ are N and Z² is C(R⁴). In some embodiments is a compound of Formula (Ia), or a pharmaceutically acceptable salt or solvate thereof, wherein Z¹ and Z³ are C(R⁴) and Z² is N. In some embodiments is a compound of Formula (Ia), or a pharmaceutically acceptable salt or solvate thereof, wherein Z² and Z³ are C(R⁴) and Z¹ is N.

[0068] In some embodiments is a compound of Formula (Ia), or a pharmaceutically acceptable salt or solvate thereof, wherein each R⁴ is independently selected from hydrogen, halogen, -CN, -OR¹⁰, C₁₋₆alkyl, C₁₋₆haloalkyl, and C₃₋₆cycloalkyl, wherein C₁₋₆alkyl, C₁₋₆haloalkyl, and C₃₋₆cycloalkyl are optionally substituted with 1-5 R^{5d} groups. In some embodiments is a compound of Formula (Ia), or a pharmaceutically acceptable salt or solvate thereof, wherein each R⁴ is independently selected from hydrogen, halogen, and unsubstituted C₁₋₆alkyl. In some embodiments is a compound of Formula (Ia), or a pharmaceutically acceptable salt or solvate thereof, wherein each R⁴ is independently selected from hydrogen and halogen. In some

embodiments is a compound of Formula (Ia), or a pharmaceutically acceptable salt or solvate thereof, wherein each R^4 is hydrogen.

[0069] In some embodiments, described herein is a compound of Formula (II), or a pharmaceutically acceptable salt or solvate thereof:



Formula (II);

wherein,

Y^1 , Y^2 , and Y^3 are each independently $C(R^3)$ or N, wherein at least one of Y^1 , Y^2 , and Y^3 is $C(R^3)$;

Z^1 , Z^2 , and Z^3 are each independently $C(R^4)$ or N, wherein at least one of Z^1 , Z^2 , and Z^3 is $C(R^4)$;

R^1 is selected from halogen, -CN, -OR¹⁰, -SR¹⁰, -N(R¹⁰)(R¹¹), C₁₋₆alkyl, C₁₋₆haloalkyl, C₂₋₆alkenyl, C₂₋₆alkynyl, C₃₋₆cycloalkyl, C₂₋₉heterocycloalkyl, C₆₋₁₀aryl, and C₁₋₉heteroaryl, wherein C₁₋₆alkyl, C₁₋₆haloalkyl, C₂₋₆alkenyl, C₂₋₆alkynyl, C₃₋₆cycloalkyl, C₂₋₉heterocycloalkyl, C₆₋₁₀aryl, and C₁₋₉heteroaryl are optionally substituted with 1-5 R^{5a} groups;

each R^2 is independently selected from halogen, -CN, -OR¹⁰, -SR¹⁰, -N(R¹⁰)(R¹¹), C₁₋₆alkyl, C₁₋₆haloalkyl, C₂₋₆alkenyl, C₂₋₆alkynyl, C₃₋₆cycloalkyl, C₂₋₉heterocycloalkyl, C₆₋₁₀aryl, and C₁₋₉heteroaryl, wherein C₁₋₆alkyl, C₁₋₆haloalkyl, C₂₋₆alkenyl, C₂₋₆alkynyl, C₃₋₆cycloalkyl, C₂₋₉heterocycloalkyl, C₆₋₁₀aryl, and C₁₋₉heteroaryl are optionally substituted with 1-5 R^{5b} groups; or two R^2 groups on different carbon atoms are taken together to form a bridge that is -CH₂CH₂-;

each R^3 is independently selected from hydrogen, halogen, -CN, -SR¹⁰, -N(R¹⁰)(R¹¹), C₁₋₆alkyl, C₁₋₆haloalkyl, C₁₋₆alkoxy, C₂₋₆alkenyl, C₂₋₆alkynyl, C₃₋₆cycloalkyl, C₂₋₉heterocycloalkyl, C₆₋₁₀aryl, and C₁₋₉heteroaryl, wherein C₁₋₆alkyl, C₁₋₆haloalkyl, C₁₋₆alkoxy, C₂₋₆alkenyl, C₂₋₆alkynyl, C₃₋₆cycloalkyl, C₂₋₉heterocycloalkyl, C₆₋₁₀aryl, and C₁₋₉heteroaryl are optionally substituted with 1-5 R^{5c} groups;

each R^4 is independently selected from hydrogen, halogen, -CN, -OR¹⁰, -SR¹⁰, -N(R¹⁰)(R¹¹), C₁₋₆alkyl, C₁₋₆haloalkyl, C₂₋₆alkenyl, C₂₋₆alkynyl, C₃₋₆cycloalkyl, C₂₋₉heterocycloalkyl, C₆₋₁₀aryl, and C₁₋₉heteroaryl, wherein C₁₋₆alkyl, C₁₋₆haloalkyl, C₂₋₆alkenyl, C₂₋₆alkynyl,

C₃₋₆cycloalkyl, C₂₋₉heterocycloalkyl, C₆₋₁₀aryl, and C₁₋₉heteroaryl are optionally substituted with 1-5 R^{5d} groups;

each R^{5a}, R^{5b}, R^{5c}, and R^{5d} is each independently selected from halogen, oxo, -CN, C₁₋₆alkyl, C₁₋₆haloalkyl, C₂₋₆alkenyl, C₂₋₆alkynyl, C₃₋₆cycloalkyl, -CH₂-C₃₋₆cycloalkyl, C₂₋₉heterocycloalkyl, -CH₂-C₂₋₉heterocycloalkyl, C₆₋₁₀aryl, -CH₂-C₆₋₁₀aryl, C₁₋₉heteroaryl, -CH₂-C₁₋₉heteroaryl, -OR¹⁰, -SR¹⁰, -N(R¹⁰)(R¹¹), -C(O)OR¹⁰, -OC(O)N(R¹⁰)(R¹¹), -N(R¹²)C(O)N(R¹⁰)(R¹¹), -N(R¹²)C(O)OR¹³, -N(R¹²)S(O)₂R¹³, -C(O)R¹³, -S(O)R¹³, -OC(O)R¹³, -C(O)N(R¹⁰)(R¹¹), -C(O)C(O)N(R¹⁰)(R¹¹), -N(R¹²)C(O)R¹³, -S(O)₂R¹³, -S(O)₂N(R¹⁰)(R¹¹), -S(=O)(=NH)N(R¹⁰)(R¹¹), -C(=NOR¹¹)R¹³, -CH₂C(O)N(R¹⁰)(R¹¹), -CH₂N(R¹²)C(O)R¹³, -CH₂S(O)₂R¹³, and -CH₂S(O)₂N(R¹⁰)(R¹¹), wherein C₁₋₆alkyl, C₁₋₆haloalkyl, C₂₋₆alkenyl, C₂₋₆alkynyl, C₃₋₆cycloalkyl, -CH₂-C₃₋₆cycloalkyl, C₂₋₉heterocycloalkyl, -CH₂-C₂₋₉heterocycloalkyl, C₆₋₁₀aryl, -CH₂-C₆₋₁₀aryl, C₁₋₉heteroaryl, -CH₂-C₁₋₉heteroaryl are optionally substituted with one, two, or three groups selected from halogen, -CN, C₁₋₆alkyl, C₁₋₆haloalkyl, C₃₋₆cycloalkyl, C₂₋₉heterocycloalkyl, C₆₋₁₀aryl, C₁₋₉heteroaryl, -OR¹⁰, and -N(R¹⁰)(R¹¹);

each R¹⁰ is independently selected from hydrogen, C₁₋₆alkyl, C₁₋₆haloalkyl, C₂₋₆alkenyl, C₂₋₆alkynyl, C₃₋₆cycloalkyl, C₂₋₉heterocycloalkyl, C₆₋₁₀aryl, and C₁₋₉heteroaryl, wherein C₁₋₆alkyl, C₂₋₆alkenyl, C₂₋₆alkynyl, C₃₋₆cycloalkyl, C₂₋₉heterocycloalkyl, C₆₋₁₀aryl, and C₁₋₉heteroaryl are optionally substituted with one, two, or three groups selected from halogen, -CN, hydroxy, C₁₋₆alkyl, C₁₋₆haloalkyl, C₁₋₆alkoxy, C₃₋₆cycloalkyl, C₂₋₉heterocycloalkyl, C₆₋₁₀aryl, and C₁₋₉heteroaryl;

each R¹¹ is independently selected from hydrogen, C₁₋₆alkyl, and C₁₋₆haloalkyl;

each R¹² is independently selected from hydrogen, C₁₋₆alkyl, and C₁₋₆haloalkyl;

each R¹³ is independently selected C₁₋₆alkyl, C₂₋₆alkenyl, C₂₋₆alkynyl, C₃₋₆cycloalkyl, C₂₋₉heterocycloalkyl, C₆₋₁₀aryl, and C₁₋₉heteroaryl, wherein C₁₋₆alkyl, C₂₋₆alkenyl, C₂₋₆alkynyl, C₃₋₆cycloalkyl, C₂₋₉heterocycloalkyl, C₆₋₁₀aryl, and C₁₋₉heteroaryl are optionally substituted with one, two, or three groups selected from halogen, -CN, hydroxy, C₁₋₆alkyl, C₁₋₆haloalkyl, C₁₋₆alkoxy, C₃₋₆cycloalkyl, C₂₋₉heterocycloalkyl, C₆₋₁₀aryl, and C₁₋₉heteroaryl; and

n is 1, 2, 3, or 4.

[0070] In some embodiments is a compound of Formula (II), or a pharmaceutically acceptable salt or solvate thereof, wherein Y¹, Y², and Y³ are each C(R³). In some embodiments is a compound of Formula (II), or a pharmaceutically acceptable salt or solvate thereof, wherein Y¹ and Y³ are C(R³) and Y² is N. In some embodiments is a compound of Formula (II), or a

pharmaceutically acceptable salt or solvate thereof, wherein Y^1 and Y^2 are $C(R^3)$ and Y^3 is N. In some embodiments is a compound of Formula (II), or a pharmaceutically acceptable salt or solvate thereof, wherein Y^2 and Y^3 are $C(R^3)$ and Y^1 is N.

[0071] In some embodiments is a compound of Formula (II), or a pharmaceutically acceptable salt or solvate thereof, wherein each R^3 is independently selected from hydrogen, halogen, -CN, - $N(R^{10})(R^{11})$, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} alkoxy, and C_{3-6} cycloalkyl, wherein C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} alkoxy, and C_{3-6} cycloalkyl are optionally substituted with 1-5 R^{5c} groups. In some embodiments is a compound of Formula (II), or a pharmaceutically acceptable salt or solvate thereof, wherein each R^3 is independently selected from hydrogen, halogen, -CN, C_{1-6} alkyl, C_{1-6} haloalkyl, and C_{1-6} alkoxy, wherein C_{1-6} alkyl, C_{1-6} haloalkyl, and C_{1-6} alkoxy are optionally substituted with 1-5 R^{5c} groups. In some embodiments is a compound of Formula (II), or a pharmaceutically acceptable salt or solvate thereof, wherein each R^3 is independently selected from hydrogen, halogen, -CN, C_{1-6} alkyl, C_{1-6} haloalkyl, and C_{1-6} alkoxy, wherein C_{1-6} alkyl, C_{1-6} haloalkyl, and C_{1-6} alkoxy are optionally substituted with 1-3 R^{5c} groups. In some embodiments is a compound of Formula (II), or a pharmaceutically acceptable salt or solvate thereof, wherein each R^3 is independently selected from hydrogen, halogen, -CN, unsubstituted C_{1-6} alkyl, -CF₃, and -OCH₃. In some embodiments is a compound of Formula (II), or a pharmaceutically acceptable salt or solvate thereof, wherein each R^3 is independently selected from hydrogen, halogen, and -CH₃. In some embodiments is a compound of Formula (II), or a pharmaceutically acceptable salt or solvate thereof, wherein each R^3 is hydrogen.

[0072] In some embodiments is a compound of Formula (II), or a pharmaceutically acceptable salt or solvate thereof, wherein each R^2 is independently selected from -OR¹⁰, C_{1-6} alkyl, and C_{1-6} haloalkyl, wherein C_{1-6} alkyl and C_{1-6} haloalkyl are optionally substituted with 1-5 R^{5b} groups. In some embodiments is a compound of Formula (II), or a pharmaceutically acceptable salt or solvate thereof, wherein each R^2 is independently selected from C_{1-6} alkyl optionally substituted with 1-5 R^{5b} groups. In some embodiments is a compound of Formula (II), or a pharmaceutically acceptable salt or solvate thereof, wherein each R^2 is independently selected from C_{1-6} alkyl optionally substituted with -OH. In some embodiments is a compound of Formula (II), or a pharmaceutically acceptable salt or solvate thereof, wherein each R^2 is -CH₂OH. In some embodiments is a compound of Formula (II), or a pharmaceutically acceptable salt or solvate thereof, wherein each R^2 is independently selected from unsubstituted C_{1-6} alkyl. In some embodiments is a compound of Formula (II), or a pharmaceutically acceptable salt or solvate thereof, wherein each R^2 is -CH₃. In some embodiments is a compound of Formula (II), or a pharmaceutically acceptable salt or solvate thereof, wherein each R^2 is -CH₂CH₃. In some

embodiments is a compound of Formula (II), or a pharmaceutically acceptable salt or solvate thereof, wherein each R^2 is $-\text{CH}(\text{CH}_3)_2$. In some embodiments is a compound of Formula (II), or a pharmaceutically acceptable salt or solvate thereof, wherein each R^2 is independently selected from $-\text{OR}^{10}$, wherein R^{10} is C_{1-6} alkyl. In some embodiments is a compound of Formula (II), or a pharmaceutically acceptable salt or solvate thereof, wherein each R^2 is $-\text{OCH}_3$.

[0073] In some embodiments is a compound of Formula (II), or a pharmaceutically acceptable salt or solvate thereof, wherein n is 1. In some embodiments is a compound of Formula (II), or a pharmaceutically acceptable salt or solvate thereof, wherein n is 2. In some embodiments is a compound of Formula (II), or a pharmaceutically acceptable salt or solvate thereof, wherein n is 3. In some embodiments is a compound of Formula (II), or a pharmaceutically acceptable salt or solvate thereof, wherein n is 4.

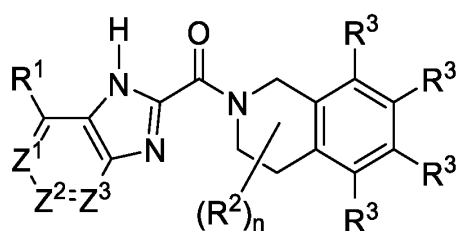
[0074] In some embodiments is a compound of Formula (II), or a pharmaceutically acceptable salt or solvate thereof, wherein R^1 is selected from halogen, $-\text{CN}$, $-\text{OR}^{10}$, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{6-10} aryl, and C_{1-9} heteroaryl, wherein C_{1-6} alkyl and C_{1-6} haloalkyl are optionally substituted with 1-5 R^{5a} groups. In some embodiments is a compound of Formula (II), or a pharmaceutically acceptable salt or solvate thereof, wherein R^1 is selected from halogen, $-\text{CN}$, $-\text{OR}^{10}$, C_{1-6} alkyl, and C_{1-6} haloalkyl wherein C_{1-6} alkyl and C_{1-6} haloalkyl are optionally substituted with 1-5 R^{5a} groups. In some embodiments is a compound of Formula (II), or a pharmaceutically acceptable salt or solvate thereof, wherein R^1 is selected from halogen, $-\text{CN}$, $-\text{OR}^{10}$, unsubstituted C_{1-6} alkyl, and unsubstituted C_{1-6} haloalkyl. In some embodiments is a compound of Formula (II), or a pharmaceutically acceptable salt or solvate thereof, wherein R^1 is halogen. In some embodiments is a compound of Formula (II), or a pharmaceutically acceptable salt or solvate thereof, wherein R^1 is $-\text{CN}$. In some embodiments is a compound of Formula (II), or a pharmaceutically acceptable salt or solvate thereof, wherein R^1 is $-\text{OR}^{10}$. In some embodiments is a compound of Formula (II), or a pharmaceutically acceptable salt or solvate thereof, wherein R^1 is $-\text{OR}^{10}$, wherein R^{10} is hydrogen C_{1-6} alkyl. In some embodiments is a compound of Formula (II), or a pharmaceutically acceptable salt or solvate thereof, wherein R^1 is $-\text{OH}$. In some embodiments is a compound of Formula (II), or a pharmaceutically acceptable salt or solvate thereof, wherein R^1 is $-\text{OCH}_3$. In some embodiments is a compound of Formula (II), or a pharmaceutically acceptable salt or solvate thereof, wherein R^1 is unsubstituted C_{1-6} alkyl. In some embodiments is a compound of Formula (II), or a pharmaceutically acceptable salt or solvate thereof, wherein R^1 is $-\text{CH}_3$. In some embodiments is a compound of Formula (II), or a pharmaceutically acceptable salt or solvate thereof, wherein R^1 is unsubstituted C_{1-6} haloalkyl. In some embodiments is a compound of Formula (II), or a pharmaceutically acceptable salt or solvate thereof, wherein R^1 is

-CF₃. In some embodiments is a compound of Formula (II), or a pharmaceutically acceptable salt or solvate thereof, wherein R¹ is selected from halogen, -CN, -OH, -OCH₃, -CH₃, and -CF₃.

[0075] In some embodiments is a compound of Formula (II), or a pharmaceutically acceptable salt or solvate thereof, wherein Z¹, Z², and Z³ are each independently C(R⁴). In some embodiments is a compound of Formula (II), or a pharmaceutically acceptable salt or solvate thereof, wherein Z¹ and Z² are C(R⁴) and Z³ is N. In some embodiments is a compound of Formula (II), or a pharmaceutically acceptable salt or solvate thereof, wherein Z¹ and Z³ are N and Z² is C(R⁴). In some embodiments is a compound of Formula (II), or a pharmaceutically acceptable salt or solvate thereof, wherein Z¹ and Z³ are C(R⁴) and Z² is N. In some embodiments is a compound of Formula (II), or a pharmaceutically acceptable salt or solvate thereof, wherein Z² and Z³ are C(R⁴) and Z¹ is N.

[0076] In some embodiments is a compound of Formula (II), or a pharmaceutically acceptable salt or solvate thereof, wherein each R⁴ is independently selected from hydrogen, halogen, -CN, -OR¹⁰, C₁₋₆alkyl, C₁₋₆haloalkyl, and C₃₋₆cycloalkyl, wherein C₁₋₆alkyl, C₁₋₆haloalkyl, and C₃₋₆cycloalkyl are optionally substituted with 1-5 R^{5d} groups. In some embodiments is a compound of Formula (II), or a pharmaceutically acceptable salt or solvate thereof, wherein each R⁴ is independently selected from hydrogen, halogen, and unsubstituted C₁₋₆alkyl. In some embodiments is a compound of Formula (II), or a pharmaceutically acceptable salt or solvate thereof, wherein each R⁴ is independently selected from hydrogen and halogen. In some embodiments is a compound of Formula (II), or a pharmaceutically acceptable salt or solvate thereof, wherein each R⁴ is hydrogen.

[0077] In some embodiments, described herein is a compound of Formula (IIa), or a pharmaceutically acceptable salt or solvate thereof:



Formula (IIa);

wherein,

Z¹, Z², and Z³ are each independently C(R⁴) or N, wherein at least one of Z¹, Z², and Z³ is C(R⁴);

R¹ is selected from halogen, -CN, -OR¹⁰, -SR¹⁰, -N(R¹⁰)(R¹¹), C₁₋₆alkyl, C₁₋₆haloalkyl, C₂₋₆alkenyl, C₂₋₆alkynyl, C₃₋₆cycloalkyl, C₂₋₉heterocycloalkyl, C₆₋₁₀aryl, and C₁₋₉heteroaryl,

wherein C₁₋₆alkyl, C₁₋₆haloalkyl, C₂₋₆alkenyl, C₂₋₆alkynyl, C₃₋₆cycloalkyl, C₂₋₉heterocycloalkyl, C₆₋₁₀aryl, and C₁₋₉heteroaryl are optionally substituted with 1-5 R^{5a} groups;

each R² is independently selected from halogen, -CN, -OR¹⁰, -SR¹⁰, -N(R¹⁰)(R¹¹), C₁₋₆alkyl, C₁₋₆haloalkyl, C₂₋₆alkenyl, C₂₋₆alkynyl, C₃₋₆cycloalkyl, C₂₋₉heterocycloalkyl, C₆₋₁₀aryl, and C₁₋₉heteroaryl, wherein C₁₋₆alkyl, C₁₋₆haloalkyl, C₂₋₆alkenyl, C₂₋₆alkynyl, C₃₋₆cycloalkyl, C₂₋₉heterocycloalkyl, C₆₋₁₀aryl, and C₁₋₉heteroaryl are optionally substituted with 1-5 R^{5b} groups; or two R² groups on different carbon atoms are taken together to form a bridge that is -CH₂CH₂-;

each R³ is independently selected from hydrogen, halogen, -CN, -SR¹⁰, -N(R¹⁰)(R¹¹), C₁₋₆alkyl, C₁₋₆haloalkyl, C₁₋₆alkoxy, C₂₋₆alkenyl, C₂₋₆alkynyl, C₃₋₆cycloalkyl, C₂₋₉heterocycloalkyl, C₆₋₁₀aryl, and C₁₋₉heteroaryl, wherein C₁₋₆alkyl, C₁₋₆haloalkyl, C₁₋₆alkoxy, C₂₋₆alkenyl, C₂₋₆alkynyl, C₃₋₆cycloalkyl, C₂₋₉heterocycloalkyl, C₆₋₁₀aryl, and C₁₋₉heteroaryl are optionally substituted with 1-5 R^{5c} groups;

each R⁴ is independently selected from hydrogen, halogen, -CN, -OR¹⁰, -SR¹⁰, -N(R¹⁰)(R¹¹), C₁₋₆alkyl, C₁₋₆haloalkyl, C₂₋₆alkenyl, C₂₋₆alkynyl, C₃₋₆cycloalkyl, C₂₋₉heterocycloalkyl, C₆₋₁₀aryl, and C₁₋₉heteroaryl, wherein C₁₋₆alkyl, C₁₋₆haloalkyl, C₂₋₆alkenyl, C₂₋₆alkynyl, C₃₋₆cycloalkyl, C₂₋₉heterocycloalkyl, C₆₋₁₀aryl, and C₁₋₉heteroaryl are optionally substituted with 1-5 R^{5d} groups;

each R^{5a}, R^{5b}, R^{5c}, and R^{5d} is each independently selected from halogen, oxo, -CN, C₁₋₆alkyl, C₁₋₆haloalkyl, C₂₋₆alkenyl, C₂₋₆alkynyl, C₃₋₆cycloalkyl, -CH₂-C₃₋₆cycloalkyl, C₂₋₉heterocycloalkyl, -CH₂-C₂₋₉heterocycloalkyl, C₆₋₁₀aryl, -CH₂-C₆₋₁₀aryl, C₁₋₉heteroaryl, -CH₂-C₁₋₉heteroaryl, -OR¹⁰, -SR¹⁰, -N(R¹⁰)(R¹¹), -C(O)OR¹⁰, -OC(O)N(R¹⁰)(R¹¹), -N(R¹²)C(O)N(R¹⁰)(R¹¹), -N(R¹²)C(O)OR¹³, -N(R¹²)S(O)₂R¹³, -C(O)R¹³, -S(O)R¹³, -OC(O)R¹³, -C(O)N(R¹⁰)(R¹¹), -C(O)C(O)N(R¹⁰)(R¹¹), -N(R¹²)C(O)R¹³, -S(O)₂R¹³, -S(O)₂N(R¹⁰)(R¹¹), -S(=O)(=NH)N(R¹⁰)(R¹¹), -C(=NOR¹¹)R¹³, -CH₂C(O)N(R¹⁰)(R¹¹), -CH₂N(R¹²)C(O)R¹³, -CH₂S(O)₂R¹³, and -CH₂S(O)₂N(R¹⁰)(R¹¹), wherein C₁₋₆alkyl, C₁₋₆haloalkyl, C₂₋₆alkenyl, C₂₋₆alkynyl, C₃₋₆cycloalkyl, -CH₂-C₃₋₆cycloalkyl, C₂₋₉heterocycloalkyl, -CH₂-C₂₋₉heterocycloalkyl, C₆₋₁₀aryl, -CH₂-C₆₋₁₀aryl, C₁₋₉heteroaryl, -CH₂-C₁₋₉heteroaryl are optionally substituted with one, two, or three groups selected from halogen, -CN, C₁₋₆alkyl, C₁₋₆haloalkyl, C₃₋₆cycloalkyl, C₂₋₉heterocycloalkyl, C₆₋₁₀aryl, C₁₋₉heteroaryl, -OR¹⁰, and -N(R¹⁰)(R¹¹);

each R¹⁰ is independently selected from hydrogen, C₁₋₆alkyl, C₁₋₆haloalkyl, C₂₋₆alkenyl, C₂₋₆alkynyl, C₃₋₆cycloalkyl, C₂₋₉heterocycloalkyl, C₆₋₁₀aryl, and C₁₋₉heteroaryl, wherein C₁₋

₆alkyl, C₂₋₆alkenyl, C₂₋₆alkynyl, C₃₋₆cycloalkyl, C₂₋₉heterocycloalkyl, C₆₋₁₀aryl, and C₁₋₉heteroaryl are optionally substituted with one, two, or three groups selected from halogen, -CN, hydroxy, C₁₋₆alkyl, C₁₋₆haloalkyl, C₁₋₆alkoxy, C₃₋₆cycloalkyl, C₂₋₉heterocycloalkyl, C₆₋₁₀aryl, and C₁₋₉heteroaryl;

each R¹¹ is independently selected from hydrogen, C₁₋₆alkyl, and C₁₋₆haloalkyl;

each R¹² is independently selected from hydrogen, C₁₋₆alkyl, and C₁₋₆haloalkyl;

each R¹³ is independently selected C₁₋₆alkyl, C₂₋₆alkenyl, C₂₋₆alkynyl, C₃₋₆cycloalkyl, C₂₋₉heterocycloalkyl, C₆₋₁₀aryl, and C₁₋₉heteroaryl, wherein C₁₋₆alkyl, C₂₋₆alkenyl, C₂₋₆alkynyl, C₃₋₆cycloalkyl, C₂₋₉heterocycloalkyl, C₆₋₁₀aryl, and C₁₋₉heteroaryl are optionally substituted with one, two, or three groups selected from halogen, -CN, hydroxy, C₁₋₆alkyl, C₁₋₆haloalkyl, C₁₋₆alkoxy, C₃₋₆cycloalkyl, C₂₋₉heterocycloalkyl, C₆₋₁₀aryl, and C₁₋₉heteroaryl; and

n is 1, 2, 3, or 4.

[0078] In some embodiments is a compound of Formula (IIa), or a pharmaceutically acceptable salt or solvate thereof, wherein each R³ is independently selected from hydrogen, halogen, -CN, -N(R¹⁰)(R¹¹), C₁₋₆alkyl, C₁₋₆haloalkyl, C₁₋₆alkoxy, and C₃₋₆cycloalkyl, wherein C₁₋₆alkyl, C₁₋₆haloalkyl, C₁₋₆alkoxy, and C₃₋₆cycloalkyl are optionally substituted with 1-5 R^{5c} groups. In some embodiments is a compound of Formula (IIa), or a pharmaceutically acceptable salt or solvate thereof, wherein each R³ is independently selected from hydrogen, halogen, -CN, C₁₋₆alkyl, C₁₋₆haloalkyl, and C₁₋₆alkoxy, wherein C₁₋₆alkyl, C₁₋₆haloalkyl, and C₁₋₆alkoxy are optionally substituted with 1-5 R^{5c} groups. In some embodiments is a compound of Formula (IIa), or a pharmaceutically acceptable salt or solvate thereof, wherein each R³ is independently selected from hydrogen, halogen, -CN, C₁₋₆alkyl, C₁₋₆haloalkyl, and C₁₋₆alkoxy, wherein C₁₋₆alkyl, C₁₋₆haloalkyl, and C₁₋₆alkoxy are optionally substituted with 1-3 R^{5c} groups. In some embodiments is a compound of Formula (IIa), or a pharmaceutically acceptable salt or solvate thereof, wherein each R³ is independently selected from hydrogen, halogen, -CN, unsubstituted C₁₋₆alkyl, -CF₃, and -OCH₃. In some embodiments is a compound of Formula (IIa), or a pharmaceutically acceptable salt or solvate thereof, wherein each R³ is independently selected from hydrogen, halogen, and -CH₃. In some embodiments is a compound of Formula (IIa), or a pharmaceutically acceptable salt or solvate thereof, wherein each R³ is hydrogen.

[0079] In some embodiments is a compound of Formula (IIa), or a pharmaceutically acceptable salt or solvate thereof, wherein each R² is independently selected from -OR¹⁰, C₁₋₆alkyl, and C₁₋₆haloalkyl, wherein C₁₋₆alkyl and C₁₋₆haloalkyl are optionally substituted with 1-5 R^{5b} groups. In some embodiments is a compound of Formula (IIa), or a pharmaceutically

acceptable salt or solvate thereof, wherein each R^2 is independently selected from C_{1-6} alkyl optionally substituted with 1-5 R^{5b} groups. In some embodiments is a compound of Formula (IIa), or a pharmaceutically acceptable salt or solvate thereof, wherein each R^2 is independently selected from C_{1-6} alkyl optionally substituted with -OH. In some embodiments is a compound of Formula (IIa), or a pharmaceutically acceptable salt or solvate thereof, wherein each R^2 is -CH₂OH. In some embodiments is a compound of Formula (IIa), or a pharmaceutically acceptable salt or solvate thereof, wherein each R^2 is independently selected from unsubstituted C_{1-6} alkyl. In some embodiments is a compound of Formula (IIa), or a pharmaceutically acceptable salt or solvate thereof, wherein each R^2 is -CH₃. In some embodiments is a compound of Formula (IIa), or a pharmaceutically acceptable salt or solvate thereof, wherein each R^2 is -CH₂CH₃. In some embodiments is a compound of Formula (IIa), or a pharmaceutically acceptable salt or solvate thereof, wherein each R^2 is -CH(CH₃)₂. In some embodiments is a compound of Formula (IIa), or a pharmaceutically acceptable salt or solvate thereof, wherein each R^2 is independently selected from -OR¹⁰, wherein R¹⁰ is C_{1-6} alkyl. In some embodiments is a compound of Formula (IIa), or a pharmaceutically acceptable salt or solvate thereof, wherein each R^2 is -OCH₃.

[0080] In some embodiments is a compound of Formula (IIa), or a pharmaceutically acceptable salt or solvate thereof, wherein n is 1. In some embodiments is a compound of Formula (IIa), or a pharmaceutically acceptable salt or solvate thereof, wherein n is 2. In some embodiments is a compound of Formula (IIa), or a pharmaceutically acceptable salt or solvate thereof, wherein n is 3. In some embodiments is a compound of Formula (IIa), or a pharmaceutically acceptable salt or solvate thereof, wherein n is 4.

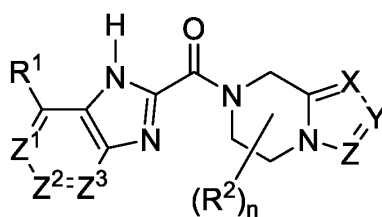
[0081] In some embodiments is a compound of Formula (IIa), or a pharmaceutically acceptable salt or solvate thereof, wherein R¹ is selected from halogen, -CN, -OR¹⁰, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{6-10} aryl, and C_{1-9} heteroaryl, wherein C_{1-6} alkyl and C_{1-6} haloalkyl are optionally substituted with 1-5 R^{5a} groups. In some embodiments is a compound of Formula (IIa), or a pharmaceutically acceptable salt or solvate thereof, wherein R¹ is selected from halogen, -CN, -OR¹⁰, C_{1-6} alkyl, and C_{1-6} haloalkyl wherein C_{1-6} alkyl and C_{1-6} haloalkyl are optionally substituted with 1-5 R^{5a} groups. In some embodiments is a compound of Formula (IIa), or a pharmaceutically acceptable salt or solvate thereof, wherein R¹ is selected from halogen, -CN, -OR¹⁰, unsubstituted C_{1-6} alkyl, and unsubstituted C_{1-6} haloalkyl. In some embodiments is a compound of Formula (IIa), or a pharmaceutically acceptable salt or solvate thereof, wherein R¹ is halogen. In some embodiments is a compound of Formula (IIa), or a pharmaceutically acceptable salt or solvate thereof, wherein R¹ is -CN. In some embodiments is a compound of Formula (IIa), or a pharmaceutically acceptable salt or solvate thereof, wherein R¹ is -OR¹⁰. In

some embodiments is a compound of Formula (IIa), or a pharmaceutically acceptable salt or solvate thereof, wherein R^1 is $-OR^{10}$, wherein R^{10} is hydrogen C_{1-6} alkyl. In some embodiments is a compound of Formula (IIa), or a pharmaceutically acceptable salt or solvate thereof, wherein R^1 is $-OH$. In some embodiments is a compound of Formula (IIa), or a pharmaceutically acceptable salt or solvate thereof, wherein R^1 is $-OCH_3$. In some embodiments is a compound of Formula (IIa), or a pharmaceutically acceptable salt or solvate thereof, wherein R^1 is unsubstituted C_{1-6} alkyl. In some embodiments is a compound of Formula (IIa), or a pharmaceutically acceptable salt or solvate thereof, wherein R^1 is $-CH_3$. In some embodiments is a compound of Formula (IIa), or a pharmaceutically acceptable salt or solvate thereof, wherein R^1 is unsubstituted C_{1-6} haloalkyl. In some embodiments is a compound of Formula (IIa), or a pharmaceutically acceptable salt or solvate thereof, wherein R^1 is $-CF_3$. In some embodiments is a compound of Formula (IIa), or a pharmaceutically acceptable salt or solvate thereof, wherein R^1 is selected from halogen, $-CN$, $-OH$, $-OCH_3$, $-CH_3$, and $-CF_3$.

[0082] In some embodiments is a compound of Formula (IIa), or a pharmaceutically acceptable salt or solvate thereof, wherein Z^1 , Z^2 , and Z^3 are each independently $C(R^4)$. In some embodiments is a compound of Formula (IIa), or a pharmaceutically acceptable salt or solvate thereof, wherein Z^1 and Z^2 are $C(R^4)$ and Z^3 is N. In some embodiments is a compound of Formula (IIa), or a pharmaceutically acceptable salt or solvate thereof, wherein Z^1 and Z^3 are N and Z^2 is $C(R^4)$. In some embodiments is a compound of Formula (IIa), or a pharmaceutically acceptable salt or solvate thereof, wherein Z^1 and Z^3 are $C(R^4)$ and Z^2 is N. In some embodiments is a compound of Formula (IIa), or a pharmaceutically acceptable salt or solvate thereof, wherein Z^2 and Z^3 are $C(R^4)$ and Z^1 is N.

[0083] In some embodiments is a compound of Formula (IIa), or a pharmaceutically acceptable salt or solvate thereof, wherein each R^4 is independently selected from hydrogen, halogen, $-CN$, $-OR^{10}$, C_{1-6} alkyl, C_{1-6} haloalkyl, and C_{3-6} cycloalkyl, wherein C_{1-6} alkyl, C_{1-6} haloalkyl, and C_{3-6} cycloalkyl are optionally substituted with 1-5 R^{5d} groups. In some embodiments is a compound of Formula (IIa), or a pharmaceutically acceptable salt or solvate thereof, wherein each R^4 is independently selected from hydrogen, halogen, and unsubstituted C_{1-6} alkyl. In some embodiments is a compound of Formula (IIa), or a pharmaceutically acceptable salt or solvate thereof, wherein each R^4 is independently selected from hydrogen and halogen. In some embodiments is a compound of Formula (IIa), or a pharmaceutically acceptable salt or solvate thereof, wherein each R^4 is hydrogen.

[0084] In some embodiments, described herein is a compound of Formula (III), or a pharmaceutically acceptable salt or solvate thereof:



Formula (III);

wherein,

X, Y and Z are each independently C(R³) or N, wherein at least one of Y and Z is C(R³);
Z¹, Z², and Z³ are each independently C(R⁴) or N, wherein at least one of Z¹, Z², and Z³ is C(R⁴);

R¹ is selected from halogen, -CN, -OR¹⁰, -SR¹⁰, -N(R¹⁰)(R¹¹), C₁₋₆alkyl, C₁₋₆haloalkyl, C₂₋₆alkenyl, C₂₋₆alkynyl, C₃₋₆cycloalkyl, C₆₋₁₀aryl, and C₁₋₉heteroaryl, wherein C₁₋₆alkyl, C₁₋₆haloalkyl, C₂₋₆alkenyl, C₂₋₆alkynyl, C₃₋₆cycloalkyl, C₆₋₁₀aryl, and C₁₋₉heteroaryl are optionally substituted with 1-5 R^{5a} groups;

each R² is independently selected from halogen, -CN, -OR¹⁰, -SR¹⁰, -N(R¹⁰)(R¹¹), C₁₋₆alkyl, C₁₋₆haloalkyl, C₂₋₆alkenyl, C₂₋₆alkynyl, C₃₋₆cycloalkyl, C₂₋₉heterocycloalkyl, C₆₋₁₀aryl, and C₁₋₉heteroaryl, wherein C₁₋₆alkyl, C₁₋₆haloalkyl, C₂₋₆alkenyl, C₂₋₆alkynyl, C₃₋₆cycloalkyl, C₂₋₉heterocycloalkyl, C₆₋₁₀aryl, and C₁₋₉heteroaryl are optionally substituted with 1-5 R^{5b} groups;

each R³ is independently selected from hydrogen, halogen, -CN, -SR¹⁰, -N(R¹⁰)(R¹¹), C₁₋₆alkyl, C₁₋₆haloalkyl, C₁₋₆alkoxy, C₂₋₆alkenyl, C₂₋₆alkynyl, C₃₋₆cycloalkyl, C₂₋₉heterocycloalkyl, C₆₋₁₀aryl, and C₁₋₉heteroaryl, wherein C₁₋₆alkyl, C₁₋₆haloalkyl, C₁₋₆alkoxy, C₂₋₆alkenyl, C₂₋₆alkynyl, C₃₋₆cycloalkyl, C₂₋₉heterocycloalkyl, C₆₋₁₀aryl, and C₁₋₉heteroaryl are optionally substituted with 1-5 R^{5c} groups;

each R⁴ is independently selected from hydrogen, halogen, -CN, -OR¹⁰, -SR¹⁰, -N(R¹⁰)(R¹¹), C₁₋₆alkyl, C₁₋₆haloalkyl, C₂₋₆alkenyl, C₂₋₆alkynyl, C₃₋₆cycloalkyl, C₂₋₉heterocycloalkyl, C₆₋₁₀aryl, and C₁₋₉heteroaryl, wherein C₁₋₆alkyl, C₁₋₆haloalkyl, C₂₋₆alkenyl, C₂₋₆alkynyl, C₃₋₆cycloalkyl, C₂₋₉heterocycloalkyl, C₆₋₁₀aryl, and C₁₋₉heteroaryl are optionally substituted with 1-5 R^{5d} groups;

each R^{5a}, R^{5b}, R^{5c}, and R^{5d} is each independently selected from halogen, oxo, -CN, C₁₋₆alkyl, C₁₋₆haloalkyl, C₂₋₆alkenyl, C₂₋₆alkynyl, C₃₋₆cycloalkyl, -CH₂-C₃₋₆cycloalkyl, C₂₋₉heterocycloalkyl, -CH₂-C₂₋₉heterocycloalkyl, C₆₋₁₀aryl, -CH₂-C₆₋₁₀aryl, C₁₋₉heteroaryl, -CH₂-C₁₋₉heteroaryl, -OR¹⁰, -SR¹⁰, -N(R¹⁰)(R¹¹), -C(O)OR¹⁰, -OC(O)N(R¹⁰)(R¹¹), -N(R¹²)C(O)N(R¹⁰)(R¹¹), -N(R¹²)C(O)OR¹³, -N(R¹²)S(O)₂R¹³, -C(O)R¹³, -S(O)R¹³, -

OC(O)R¹³, -C(O)N(R¹⁰)(R¹¹), -C(O)C(O)N(R¹⁰)(R¹¹), -N(R¹²)C(O)R¹³, -S(O)₂R¹³, -S(O)₂N(R¹⁰)(R¹¹)-, -S(=O)(=NH)N(R¹⁰)(R¹¹), -C(=NOR¹¹)R¹³, -CH₂C(O)N(R¹⁰)(R¹¹), -CH₂N(R¹²)C(O)R¹³, -CH₂S(O)₂R¹³, and -CH₂S(O)₂N(R¹⁰)(R¹¹), wherein C₁₋₆alkyl, C₁₋₆haloalkyl, C₂₋₆alkenyl, C₂₋₆alkynyl, C₃₋₆cycloalkyl, -CH₂-C₃₋₆cycloalkyl, C₂₋₉heterocycloalkyl, -CH₂-C₂₋₉heterocycloalkyl, C₆₋₁₀aryl, -CH₂-C₆₋₁₀aryl, C₁₋₉heteroaryl, -CH₂-C₁₋₉heteroaryl are optionally substituted with one, two, or three groups selected from halogen, -CN, C₁₋₆alkyl, C₁₋₆haloalkyl, C₃₋₆cycloalkyl, C₂₋₉heterocycloalkyl, C₆₋₁₀aryl, C₁₋₉heteroaryl, -OR¹⁰, and -N(R¹⁰)(R¹¹);

each R¹⁰ is independently selected from hydrogen, C₁₋₆alkyl, C₁₋₆haloalkyl, C₂₋₆alkenyl, C₂₋₆alkynyl, C₃₋₆cycloalkyl, C₂₋₉heterocycloalkyl, C₆₋₁₀aryl, and C₁₋₉heteroaryl, wherein C₁₋₆alkyl, C₂₋₆alkenyl, C₂₋₆alkynyl, C₃₋₆cycloalkyl, C₂₋₉heterocycloalkyl, C₆₋₁₀aryl, and C₁₋₉heteroaryl are optionally substituted with one, two, or three groups selected from halogen, -CN, hydroxy, C₁₋₆alkyl, C₁₋₆haloalkyl, C₁₋₆alkoxy, C₃₋₆cycloalkyl, C₂₋₉heterocycloalkyl, C₆₋₁₀aryl, and C₁₋₉heteroaryl;

each R¹¹ is independently selected from hydrogen, C₁₋₆alkyl, and C₁₋₆haloalkyl;

each R¹² is independently selected from hydrogen, C₁₋₆alkyl, and C₁₋₆haloalkyl;

each R¹³ is independently selected C₁₋₆alkyl, C₂₋₆alkenyl, C₂₋₆alkynyl, C₃₋₆cycloalkyl, C₂₋₉heterocycloalkyl, C₆₋₁₀aryl, and C₁₋₉heteroaryl, wherein C₁₋₆alkyl, C₂₋₆alkenyl, C₂₋₆alkynyl, C₃₋₆cycloalkyl, C₂₋₉heterocycloalkyl, C₆₋₁₀aryl, and C₁₋₉heteroaryl are optionally substituted with one, two, or three groups selected from halogen, -CN, hydroxy, C₁₋₆alkyl, C₁₋₆haloalkyl, C₁₋₆alkoxy, C₃₋₆cycloalkyl, C₂₋₉heterocycloalkyl, C₆₋₁₀aryl, and C₁₋₉heteroaryl; and

n is 0, 1, 2, 3, or 4.

[0085] In some embodiments is a compound of Formula (III), or a pharmaceutically acceptable salt or solvate thereof, wherein X, Y, and Z are each C(R³). In some embodiments is a compound of Formula (III), or a pharmaceutically acceptable salt or solvate thereof, wherein X and Z are C(R³) and Y is N. In some embodiments is a compound of Formula (III), or a pharmaceutically acceptable salt or solvate thereof, wherein X and Y are C(R³) and Z is N. In some embodiments is a compound of Formula (III), or a pharmaceutically acceptable salt or solvate thereof, wherein X is N and Y and Z are C(R³). In some embodiments is a compound of Formula (III), or a pharmaceutically acceptable salt or solvate thereof, wherein X and Y are N and Z is C(R³).

[0086] In some embodiments is a compound of Formula (III), or a pharmaceutically acceptable salt or solvate thereof, wherein each R³ is independently selected from hydrogen, halogen, -CN, -N(R¹⁰)(R¹¹), C₁₋₆alkyl, C₁₋₆haloalkyl, C₁₋₆alkoxy, and C₃₋₆cycloalkyl, wherein C₁₋₆alkyl, C₁₋₆haloalkyl, C₁₋₆alkoxy, and C₃₋₆cycloalkyl are optionally substituted with one, two, or three groups selected from halogen, -CN, hydroxy, C₁₋₆alkyl, C₁₋₆haloalkyl, C₁₋₆alkoxy, C₃₋₆cycloalkyl, C₂₋₉heterocycloalkyl, C₆₋₁₀aryl, and C₁₋₉heteroaryl;

haloalkyl, C₁₋₆alkoxy, and C₃₋₆cycloalkyl are optionally substituted with 1-5 R^{5c} groups. In some embodiments is a compound of Formula (III), or a pharmaceutically acceptable salt or solvate thereof, wherein each R³ is independently selected from hydrogen, halogen, -CN, C₁₋₆alkyl, C₁₋₆haloalkyl, and C₁₋₆alkoxy, wherein C₁₋₆alkyl, C₁₋₆haloalkyl, and C₁₋₆alkoxy are optionally substituted with 1-5 R^{5c} groups. In some embodiments is a compound of Formula (III), or a pharmaceutically acceptable salt or solvate thereof, wherein each R³ is independently selected from hydrogen, halogen, -CN, C₁₋₆alkyl, C₁₋₆haloalkyl, and C₁₋₆alkoxy, wherein C₁₋₆alkyl, C₁₋₆haloalkyl, and C₁₋₆alkoxy are optionally substituted with 1-3 R^{5c} groups. In some embodiments is a compound of Formula (III), or a pharmaceutically acceptable salt or solvate thereof, wherein each R³ is independently selected from hydrogen, halogen, -CN, unsubstituted C₁₋₆alkyl, -CF₃, and -OCH₃. In some embodiments is a compound of Formula (III), or a pharmaceutically acceptable salt or solvate thereof, wherein each R³ is independently selected from hydrogen, halogen, and -CH₃. In some embodiments is a compound of Formula (III), or a pharmaceutically acceptable salt or solvate thereof, wherein each R³ is hydrogen.

[0087] In some embodiments is a compound of Formula (III), or a pharmaceutically acceptable salt or solvate thereof, wherein each R² is independently selected from -OR¹⁰, C₁₋₆alkyl, and C₁₋₆haloalkyl, wherein C₁₋₆alkyl and C₁₋₆haloalkyl are optionally substituted with 1-5 R^{5b} groups. In some embodiments is a compound of Formula (III), or a pharmaceutically acceptable salt or solvate thereof, wherein each R² is independently selected from C₁₋₆alkyl optionally substituted with 1-5 R^{5b} groups. In some embodiments is a compound of Formula (III), or a pharmaceutically acceptable salt or solvate thereof, wherein each R² is independently selected from C₁₋₆alkyl optionally substituted with -OH. In some embodiments is a compound of Formula (III), or a pharmaceutically acceptable salt or solvate thereof, wherein each R² is -CH₂OH. In some embodiments is a compound of Formula (III), or a pharmaceutically acceptable salt or solvate thereof, wherein each R² is independently selected from unsubstituted C₁₋₆alkyl. In some embodiments is a compound of Formula (III), or a pharmaceutically acceptable salt or solvate thereof, wherein each R² is -CH₃. In some embodiments is a compound of Formula (III), or a pharmaceutically acceptable salt or solvate thereof, wherein each R² is -CH₂CH₃. In some embodiments is a compound of Formula (III), or a pharmaceutically acceptable salt or solvate thereof, wherein each R² is -CH(CH₃)₂. In some embodiments is a compound of Formula (III), or a pharmaceutically acceptable salt or solvate thereof, wherein each R² is independently selected from -OR¹⁰, wherein R¹⁰ is C₁₋₆alkyl. In some embodiments is a compound of Formula (III), or a pharmaceutically acceptable salt or solvate thereof, wherein each R² is -OCH₃.

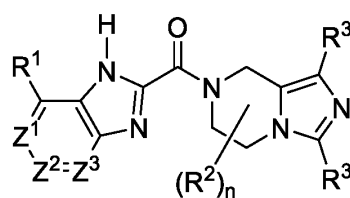
[0088] In some embodiments is a compound of Formula (III), or a pharmaceutically acceptable salt or solvate thereof, wherein n is 1. In some embodiments is a compound of Formula (III), or a pharmaceutically acceptable salt or solvate thereof, wherein n is 2. In some embodiments is a compound of Formula (III), or a pharmaceutically acceptable salt or solvate thereof, wherein n is 3. In some embodiments is a compound of Formula (III), or a pharmaceutically acceptable salt or solvate thereof, wherein n is 4. In some embodiments is a compound of Formula (III), or a pharmaceutically acceptable salt or solvate thereof, wherein n is 0.

[0089] In some embodiments is a compound of Formula (III), or a pharmaceutically acceptable salt or solvate thereof, wherein R¹ is selected from halogen, -CN, -OR¹⁰, C₁₋₆alkyl, C₁₋₆haloalkyl, C₆₋₁₀aryl, and C₁₋₉heteroaryl, wherein C₁₋₆alkyl and C₁₋₆haloalkyl are optionally substituted with 1-5 R^{5a} groups. In some embodiments is a compound of Formula (III), or a pharmaceutically acceptable salt or solvate thereof, wherein R¹ is selected from halogen, -CN, -OR¹⁰, C₁₋₆alkyl, and C₁₋₆haloalkyl wherein C₁₋₆alkyl and C₁₋₆haloalkyl are optionally substituted with 1-5 R^{5a} groups. In some embodiments is a compound of Formula (III), or a pharmaceutically acceptable salt or solvate thereof, wherein R¹ is selected from halogen, -CN, -OR¹⁰, unsubstituted C₁₋₆alkyl, and unsubstituted C₁₋₆haloalkyl. In some embodiments is a compound of Formula (III), or a pharmaceutically acceptable salt or solvate thereof, wherein R¹ is halogen. In some embodiments is a compound of Formula (III), or a pharmaceutically acceptable salt or solvate thereof, wherein R¹ is -CN. In some embodiments is a compound of Formula (III), or a pharmaceutically acceptable salt or solvate thereof, wherein R¹ is -OR¹⁰. In some embodiments is a compound of Formula (III), or a pharmaceutically acceptable salt or solvate thereof, wherein R¹ is -OR¹⁰, wherein R¹⁰ is hydrogen C₁₋₆alkyl. In some embodiments is a compound of Formula (III), or a pharmaceutically acceptable salt or solvate thereof, wherein R¹ is -OH. In some embodiments is a compound of Formula (III), or a pharmaceutically acceptable salt or solvate thereof, wherein R¹ is -OCH₃. In some embodiments is a compound of Formula (III), or a pharmaceutically acceptable salt or solvate thereof, wherein R¹ is unsubstituted C₁₋₆alkyl. In some embodiments is a compound of Formula (III), or a pharmaceutically acceptable salt or solvate thereof, wherein R¹ is -CH₃. In some embodiments is a compound of Formula (III), or a pharmaceutically acceptable salt or solvate thereof, wherein R¹ is unsubstituted C₁₋₆haloalkyl. In some embodiments is a compound of Formula (III), or a pharmaceutically acceptable salt or solvate thereof, wherein R¹ is -CF₃. In some embodiments is a compound of Formula (III), or a pharmaceutically acceptable salt or solvate thereof, wherein R¹ is selected from halogen, -CN, -OH, -OCH₃, -CH₃, and -CF₃.

[0090] In some embodiments is a compound of Formula (III), or a pharmaceutically acceptable salt or solvate thereof, wherein Z^1 , Z^2 , and Z^3 are each independently $C(R^4)$. In some embodiments is a compound of Formula (III), or a pharmaceutically acceptable salt or solvate thereof, wherein Z^1 and Z^2 are $C(R^4)$ and Z^3 is N. In some embodiments is a compound of Formula (III), or a pharmaceutically acceptable salt or solvate thereof, wherein Z^1 and Z^3 are N and Z^2 is $C(R^4)$. In some embodiments is a compound of Formula (III), or a pharmaceutically acceptable salt or solvate thereof, wherein Z^1 and Z^3 are $C(R^4)$ and Z^2 is N. In some embodiments is a compound of Formula (III), or a pharmaceutically acceptable salt or solvate thereof, wherein Z^2 and Z^3 are $C(R^4)$ and Z^1 is N.

[0091] In some embodiments is a compound of Formula (III), or a pharmaceutically acceptable salt or solvate thereof, wherein each R^4 is independently selected from hydrogen, halogen, $-CN$, $-OR^{10}$, C_{1-6} alkyl, C_{1-6} haloalkyl, and C_{3-6} cycloalkyl, wherein C_{1-6} alkyl, C_{1-6} haloalkyl, and C_{3-6} cycloalkyl are optionally substituted with 1-5 R^{5d} groups. In some embodiments is a compound of Formula (III), or a pharmaceutically acceptable salt or solvate thereof, wherein each R^4 is independently selected from hydrogen, halogen, and unsubstituted C_{1-6} alkyl. In some embodiments is a compound of Formula (III), or a pharmaceutically acceptable salt or solvate thereof, wherein each R^4 is independently selected from hydrogen and halogen. In some embodiments is a compound of Formula (III), or a pharmaceutically acceptable salt or solvate thereof, wherein each R^4 is hydrogen.

[0092] In some embodiments, described herein is a compound of Formula (IIIa), or a pharmaceutically acceptable salt or solvate thereof:



Formula (IIIa);

wherein,

Z^1 , Z^2 , and Z^3 are each independently $C(R^4)$ or N, wherein at least one of Z^1 , Z^2 , and Z^3 is $C(R^4)$;

R^1 is selected from halogen, $-CN$, $-OR^{10}$, $-SR^{10}$, $-N(R^{10})(R^{11})$, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-6} cycloalkyl, C_{6-10} aryl, and C_{1-9} heteroaryl, wherein C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-6} cycloalkyl, C_{6-10} aryl, and C_{1-9} heteroaryl are optionally substituted with 1-5 R^{5a} groups;

each R² is independently selected from halogen, -CN, -OR¹⁰, -SR¹⁰, -N(R¹⁰)(R¹¹), C₁₋₆alkyl, C₁₋₆haloalkyl, C₂₋₆alkenyl, C₂₋₆alkynyl, C₃₋₆cycloalkyl, C₂₋₉heterocycloalkyl, C₆₋₁₀aryl, and C₁₋₉heteroaryl, wherein C₁₋₆alkyl, C₁₋₆haloalkyl, C₂₋₆alkenyl, C₂₋₆alkynyl, C₃₋₆cycloalkyl, C₂₋₉heterocycloalkyl, C₆₋₁₀aryl, and C₁₋₉heteroaryl are optionally substituted with 1-5 R^{5b} groups;

each R³ is independently selected from hydrogen, halogen, -CN, -SR¹⁰, -N(R¹⁰)(R¹¹), C₁₋₆alkyl, C₁₋₆haloalkyl, C₁₋₆alkoxy, C₂₋₆alkenyl, C₂₋₆alkynyl, C₃₋₆cycloalkyl, C₂₋₉heterocycloalkyl, C₆₋₁₀aryl, and C₁₋₉heteroaryl, wherein C₁₋₆alkyl, C₁₋₆haloalkyl, C₁₋₆alkoxy, C₂₋₆alkenyl, C₂₋₆alkynyl, C₃₋₆cycloalkyl, C₂₋₉heterocycloalkyl, C₆₋₁₀aryl, and C₁₋₉heteroaryl are optionally substituted with 1-5 R^{5c} groups;

each R⁴ is independently selected from hydrogen, halogen, -CN, -OR¹⁰, -SR¹⁰, -N(R¹⁰)(R¹¹), C₁₋₆alkyl, C₁₋₆haloalkyl, C₂₋₆alkenyl, C₂₋₆alkynyl, C₃₋₆cycloalkyl, C₂₋₉heterocycloalkyl, C₆₋₁₀aryl, and C₁₋₉heteroaryl, wherein C₁₋₆alkyl, C₁₋₆haloalkyl, C₂₋₆alkenyl, C₂₋₆alkynyl, C₃₋₆cycloalkyl, C₂₋₉heterocycloalkyl, C₆₋₁₀aryl, and C₁₋₉heteroaryl are optionally substituted with 1-5 R^{5d} groups;

each R^{5a}, R^{5b}, R^{5c}, and R^{5d} is each independently selected from halogen, oxo, -CN, C₁₋₆alkyl, C₁₋₆haloalkyl, C₂₋₆alkenyl, C₂₋₆alkynyl, C₃₋₆cycloalkyl, -CH₂-C₃₋₆cycloalkyl, C₂₋₉heterocycloalkyl, -CH₂-C₂₋₉heterocycloalkyl, C₆₋₁₀aryl, -CH₂-C₆₋₁₀aryl, C₁₋₉heteroaryl, -CH₂-C₁₋₉heteroaryl, -OR¹⁰, -SR¹⁰, -N(R¹⁰)(R¹¹), -C(O)OR¹⁰, -OC(O)N(R¹⁰)(R¹¹), -N(R¹²)C(O)N(R¹⁰)(R¹¹), -N(R¹²)C(O)OR¹³, -N(R¹²)S(O)₂R¹³, -C(O)R¹³, -S(O)R¹³, -OC(O)R¹³, -C(O)N(R¹⁰)(R¹¹), -C(O)C(O)N(R¹⁰)(R¹¹), -N(R¹²)C(O)R¹³, -S(O)₂R¹³, -S(O)₂N(R¹⁰)(R¹¹), -S(=O)(=NH)N(R¹⁰)(R¹¹), -C(=NOR¹¹)R¹³, -CH₂C(O)N(R¹⁰)(R¹¹), -CH₂N(R¹²)C(O)R¹³, -CH₂S(O)₂R¹³, and -CH₂S(O)₂N(R¹⁰)(R¹¹), wherein C₁₋₆alkyl, C₁₋₆haloalkyl, C₂₋₆alkenyl, C₂₋₆alkynyl, C₃₋₆cycloalkyl, -CH₂-C₃₋₆cycloalkyl, C₂₋₉heterocycloalkyl, -CH₂-C₂₋₉heterocycloalkyl, C₆₋₁₀aryl, -CH₂-C₆₋₁₀aryl, C₁₋₉heteroaryl, -CH₂-C₁₋₉heteroaryl are optionally substituted with one, two, or three groups selected from halogen, -CN, C₁₋₆alkyl, C₁₋₆haloalkyl, C₃₋₆cycloalkyl, C₂₋₉heterocycloalkyl, C₆₋₁₀aryl, C₁₋₉heteroaryl, -OR¹⁰, and -N(R¹⁰)(R¹¹);

each R¹⁰ is independently selected from hydrogen, C₁₋₆alkyl, C₁₋₆haloalkyl, C₂₋₆alkenyl, C₂₋₆alkynyl, C₃₋₆cycloalkyl, C₂₋₉heterocycloalkyl, C₆₋₁₀aryl, and C₁₋₉heteroaryl, wherein C₁₋₆alkyl, C₂₋₆alkenyl, C₂₋₆alkynyl, C₃₋₆cycloalkyl, C₂₋₉heterocycloalkyl, C₆₋₁₀aryl, and C₁₋₉heteroaryl are optionally substituted with one, two, or three groups selected from halogen, -CN, hydroxy, C₁₋₆alkyl, C₁₋₆haloalkyl, C₁₋₆alkoxy, C₃₋₆cycloalkyl, C₂₋₉heterocycloalkyl, C₆₋₁₀aryl, and C₁₋₉heteroaryl;

each R¹¹ is independently selected from hydrogen, C₁₋₆alkyl, and C₁₋₆haloalkyl;
 each R¹² is independently selected from hydrogen, C₁₋₆alkyl, and C₁₋₆haloalkyl;
 each R¹³ is independently selected C₁₋₆alkyl, C₂₋₆alkenyl, C₂₋₆alkynyl, C₃₋₆cycloalkyl, C₂₋₉heterocycloalkyl, C₆₋₁₀aryl, and C₁₋₉heteroaryl, wherein C₁₋₆alkyl, C₂₋₆alkenyl, C₂₋₆alkynyl, C₃₋₆cycloalkyl, C₂₋₉heterocycloalkyl, C₆₋₁₀aryl, and C₁₋₉heteroaryl are optionally substituted with one, two, or three groups selected from halogen, -CN, hydroxy, C₁₋₆alkyl, C₁₋₆haloalkyl, C₁₋₆alkoxy, C₃₋₆cycloalkyl, C₂₋₉heterocycloalkyl, C₆₋₁₀aryl, and C₁₋₉heteroaryl; and
 n is 0, 1, 2, 3, or 4.

[0093] In some embodiments is a compound of Formula (IIIa), or a pharmaceutically acceptable salt or solvate thereof, wherein each R³ is independently selected from hydrogen, halogen, -CN, -N(R¹⁰)(R¹¹), C₁₋₆alkyl, C₁₋₆haloalkyl, C₁₋₆alkoxy, and C₃₋₆cycloalkyl, wherein C₁₋₆alkyl, C₁₋₆haloalkyl, C₁₋₆alkoxy, and C₃₋₆cycloalkyl are optionally substituted with 1-5 R^{5c} groups. In some embodiments is a compound of Formula (IIIa), or a pharmaceutically acceptable salt or solvate thereof, wherein each R³ is independently selected from hydrogen, halogen, -CN, C₁₋₆alkyl, C₁₋₆haloalkyl, and C₁₋₆alkoxy, wherein C₁₋₆alkyl, C₁₋₆haloalkyl, and C₁₋₆alkoxy are optionally substituted with 1-5 R^{5c} groups. In some embodiments is a compound of Formula (IIIa), or a pharmaceutically acceptable salt or solvate thereof, wherein each R³ is independently selected from hydrogen, halogen, -CN, C₁₋₆alkyl, C₁₋₆haloalkyl, and C₁₋₆alkoxy, wherein C₁₋₆alkyl, C₁₋₆haloalkyl, and C₁₋₆alkoxy are optionally substituted with 1-3 R^{5c} groups. In some embodiments is a compound of Formula (IIIa), or a pharmaceutically acceptable salt or solvate thereof, wherein each R³ is independently selected from hydrogen, halogen, -CN, unsubstituted C₁₋₆alkyl, -CF₃, and -OCH₃. In some embodiments is a compound of Formula (IIIa), or a pharmaceutically acceptable salt or solvate thereof, wherein each R³ is independently selected from hydrogen, halogen, and -CH₃. In some embodiments is a compound of Formula (IIIa), or a pharmaceutically acceptable salt or solvate thereof, wherein each R³ is hydrogen.

[0094] In some embodiments is a compound of Formula (IIIa), or a pharmaceutically acceptable salt or solvate thereof, wherein each R² is independently selected from -OR¹⁰, C₁₋₆alkyl, and C₁₋₆haloalkyl, wherein C₁₋₆alkyl and C₁₋₆haloalkyl are optionally substituted with 1-5 R^{5b} groups. In some embodiments is a compound of Formula (IIIa), or a pharmaceutically acceptable salt or solvate thereof, wherein each R² is independently selected from C₁₋₆alkyl optionally substituted with 1-5 R^{5b} groups. In some embodiments is a compound of Formula (IIIa), or a pharmaceutically acceptable salt or solvate thereof, wherein each R² is independently selected from C₁₋₆alkyl optionally substituted with -OH. In some embodiments is a compound of

Formula (IIIa), or a pharmaceutically acceptable salt or solvate thereof, wherein each R^2 is $-CH_2OH$. In some embodiments is a compound of Formula (IIIa), or a pharmaceutically acceptable salt or solvate thereof, wherein each R^2 is independently selected from unsubstituted $C_{1-6}alkyl$. In some embodiments is a compound of Formula (IIIa), or a pharmaceutically acceptable salt or solvate thereof, wherein each R^2 is $-CH_3$. In some embodiments is a compound of Formula (IIIa), or a pharmaceutically acceptable salt or solvate thereof, wherein each R^2 is $-CH_2CH_3$. In some embodiments is a compound of Formula (IIIa), or a pharmaceutically acceptable salt or solvate thereof, wherein each R^2 is $-CH(CH_3)_2$. In some embodiments is a compound of Formula (IIIa), or a pharmaceutically acceptable salt or solvate thereof, wherein each R^2 is independently selected from $-OR^{10}$, wherein R^{10} is $C_{1-6}alkyl$. In some embodiments is a compound of Formula (IIIa), or a pharmaceutically acceptable salt or solvate thereof, wherein each R^2 is $-OCH_3$.

[0095] In some embodiments is a compound of Formula (IIIa), or a pharmaceutically acceptable salt or solvate thereof, wherein n is 1. In some embodiments is a compound of Formula (IIIa), or a pharmaceutically acceptable salt or solvate thereof, wherein n is 2. In some embodiments is a compound of Formula (IIIa), or a pharmaceutically acceptable salt or solvate thereof, wherein n is 3. In some embodiments is a compound of Formula (IIIa), or a pharmaceutically acceptable salt or solvate thereof, wherein n is 4. In some embodiments is a compound of Formula (IIIa), or a pharmaceutically acceptable salt or solvate thereof, wherein n is 0.

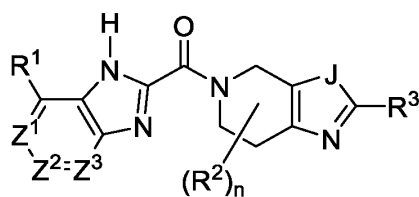
[0096] In some embodiments is a compound of Formula (IIIa), or a pharmaceutically acceptable salt or solvate thereof, wherein R^1 is selected from halogen, $-CN$, $-OR^{10}$, $C_{1-6}alkyl$, $C_{1-6}haloalkyl$, $C_{6-10}aryl$, and $C_{1-9}heteroaryl$, wherein $C_{1-6}alkyl$ and $C_{1-6}haloalkyl$ are optionally substituted with 1-5 R^{5a} groups. In some embodiments is a compound of Formula (IIIa), or a pharmaceutically acceptable salt or solvate thereof, wherein R^1 is selected from halogen, $-CN$, $-OR^{10}$, $C_{1-6}alkyl$, and $C_{1-6}haloalkyl$ wherein $C_{1-6}alkyl$ and $C_{1-6}haloalkyl$ are optionally substituted with 1-5 R^{5a} groups. In some embodiments is a compound of Formula (IIIa), or a pharmaceutically acceptable salt or solvate thereof, wherein R^1 is selected from halogen, $-CN$, $-OR^{10}$, unsubstituted $C_{1-6}alkyl$, and unsubstituted $C_{1-6}haloalkyl$. In some embodiments is a compound of Formula (IIIa), or a pharmaceutically acceptable salt or solvate thereof, wherein R^1 is halogen. In some embodiments is a compound of Formula (IIIa), or a pharmaceutically acceptable salt or solvate thereof, wherein R^1 is $-CN$. In some embodiments is a compound of Formula (IIIa), or a pharmaceutically acceptable salt or solvate thereof, wherein R^1 is $-OR^{10}$. In some embodiments is a compound of Formula (IIIa), or a pharmaceutically acceptable salt or

solvate thereof, wherein R^1 is $-OR^{10}$, wherein R^{10} is hydrogen C_{1-6} alkyl. In some embodiments is a compound of Formula (IIIa), or a pharmaceutically acceptable salt or solvate thereof, wherein R^1 is $-OH$. In some embodiments is a compound of Formula (IIIa), or a pharmaceutically acceptable salt or solvate thereof, wherein R^1 is $-OCH_3$. In some embodiments is a compound of Formula (IIIa), or a pharmaceutically acceptable salt or solvate thereof, wherein R^1 is unsubstituted C_{1-6} alkyl. In some embodiments is a compound of Formula (IIIa), or a pharmaceutically acceptable salt or solvate thereof, wherein R^1 is $-CH_3$. In some embodiments is a compound of Formula (IIIa), or a pharmaceutically acceptable salt or solvate thereof, wherein R^1 is unsubstituted C_{1-6} haloalkyl. In some embodiments is a compound of Formula (IIIa), or a pharmaceutically acceptable salt or solvate thereof, wherein R^1 is $-CF_3$. In some embodiments is a compound of Formula (IIIa), or a pharmaceutically acceptable salt or solvate thereof, wherein R^1 is selected from halogen, $-CN$, $-OH$, $-OCH_3$, $-CH_3$, and $-CF_3$.

[0097] In some embodiments is a compound of Formula (IIIa), or a pharmaceutically acceptable salt or solvate thereof, wherein Z^1 , Z^2 , and Z^3 are each independently $C(R^4)$. In some embodiments is a compound of Formula (IIIa), or a pharmaceutically acceptable salt or solvate thereof, wherein Z^1 and Z^2 are $C(R^4)$ and Z^3 is N. In some embodiments is a compound of Formula (IIIa), or a pharmaceutically acceptable salt or solvate thereof, wherein Z^1 and Z^3 are N and Z^2 is $C(R^4)$. In some embodiments is a compound of Formula (IIIa), or a pharmaceutically acceptable salt or solvate thereof, wherein Z^1 and Z^3 are $C(R^4)$ and Z^2 is N. In some embodiments is a compound of Formula (IIIa), or a pharmaceutically acceptable salt or solvate thereof, wherein Z^2 and Z^3 are $C(R^4)$ and Z^1 is N.

[0098] In some embodiments is a compound of Formula (IIIa), or a pharmaceutically acceptable salt or solvate thereof, wherein each R^4 is independently selected from hydrogen, halogen, $-CN$, $-OR^{10}$, C_{1-6} alkyl, C_{1-6} haloalkyl, and C_{3-6} cycloalkyl, wherein C_{1-6} alkyl, C_{1-6} haloalkyl, and C_{3-6} cycloalkyl are optionally substituted with 1-5 R^{5d} groups. In some embodiments is a compound of Formula (IIIa), or a pharmaceutically acceptable salt or solvate thereof, wherein each R^4 is independently selected from hydrogen, halogen, and unsubstituted C_{1-6} alkyl. In some embodiments is a compound of Formula (IIIa), or a pharmaceutically acceptable salt or solvate thereof, wherein each R^4 is independently selected from hydrogen and halogen. In some embodiments is a compound of Formula (IIIa), or a pharmaceutically acceptable salt or solvate thereof, wherein each R^4 is hydrogen.

[0099] In some embodiments, described herein is a compound of Formula (IV), or a pharmaceutically acceptable salt or solvate thereof:



Formula (IV);

wherein,

Z^1 , Z^2 , and Z^3 are each independently $C(R^4)$ or N, wherein at least one of Z^1 , Z^2 , and Z^3 is $C(R^4)$;

J is O or S;

R^1 is selected from hydrogen, halogen, -CN, -OR¹⁰, -SR¹⁰, -N(R¹⁰)(R¹¹), C₁₋₆alkyl, C₁₋₆haloalkyl, C₂₋₆alkenyl, C₂₋₆alkynyl, C₃₋₆cycloalkyl, C₂₋₉heterocycloalkyl, C₆₋₁₀aryl, and C₁₋₉heteroaryl, wherein C₁₋₆alkyl, C₁₋₆haloalkyl, C₂₋₆alkenyl, C₂₋₆alkynyl, C₃₋₆cycloalkyl, C₂₋₉heterocycloalkyl, C₆₋₁₀aryl, and C₁₋₉heteroaryl are optionally substituted with 1-5 R^{5a} groups;

each R² is independently selected from halogen, -CN, -OR¹⁰, -SR¹⁰, -N(R¹⁰)(R¹¹), C₁₋₆alkyl, C₁₋₆haloalkyl, C₂₋₆alkenyl, C₂₋₆alkynyl, C₃₋₆cycloalkyl, C₂₋₉heterocycloalkyl, C₆₋₁₀aryl, and C₁₋₉heteroaryl, wherein C₁₋₆alkyl, C₁₋₆haloalkyl, C₂₋₆alkenyl, C₂₋₆alkynyl, C₃₋₆cycloalkyl, C₂₋₉heterocycloalkyl, C₆₋₁₀aryl, and C₁₋₉heteroaryl are optionally substituted with 1-5 R^{5b} groups;

R^3 is selected from hydrogen, halogen, -CN, -SR¹⁰, -N(R¹⁰)(R¹¹), C₁₋₆alkyl, C₁₋₆haloalkyl, C₁₋₆alkoxy, C₂₋₆alkenyl, C₂₋₆alkynyl, C₃₋₆cycloalkyl, C₂₋₉heterocycloalkyl, C₆₋₁₀aryl, and C₁₋₉heteroaryl, wherein C₁₋₆alkyl, C₁₋₆haloalkyl, C₁₋₆alkoxy, C₂₋₆alkenyl, C₂₋₆alkynyl, C₃₋₆cycloalkyl, C₂₋₉heterocycloalkyl, C₆₋₁₀aryl, and C₁₋₉heteroaryl are optionally substituted with 1-5 R^{5c} groups;

each R⁴ is independently selected from hydrogen, halogen, -CN, -OR¹⁰, -SR¹⁰, -N(R¹⁰)(R¹¹), C₁₋₆alkyl, C₁₋₆haloalkyl, C₂₋₆alkenyl, C₂₋₆alkynyl, C₃₋₆cycloalkyl, C₂₋₉heterocycloalkyl, C₆₋₁₀aryl, and C₁₋₉heteroaryl, wherein C₁₋₆alkyl, C₁₋₆haloalkyl, C₂₋₆alkenyl, C₂₋₆alkynyl, C₃₋₆cycloalkyl, C₂₋₉heterocycloalkyl, C₆₋₁₀aryl, and C₁₋₉heteroaryl are optionally substituted with 1-5 R^{5d} groups;

each R^{5a}, R^{5b}, R^{5c}, and R^{5d} is each independently selected from halogen, oxo, -CN, C₁₋₆alkyl, C₁₋₆haloalkyl, C₂₋₆alkenyl, C₂₋₆alkynyl, C₃₋₆cycloalkyl, -CH₂-C₃₋₆cycloalkyl, C₂₋₉heterocycloalkyl, -CH₂-C₂₋₉heterocycloalkyl, C₆₋₁₀aryl, -CH₂-C₆₋₁₀aryl, C₁₋₉heteroaryl, -CH₂-C₁₋₉heteroaryl, -OR¹⁰, -SR¹⁰, -N(R¹⁰)(R¹¹), -C(O)OR¹⁰, -OC(O)N(R¹⁰)(R¹¹), -

$N(R^{12})C(O)N(R^{10})(R^{11})$, $-N(R^{12})C(O)OR^{13}$, $-N(R^{12})S(O)_2R^{13}$, $-C(O)R^{13}$, $-S(O)R^{13}$, $-OC(O)R^{13}$, $-C(O)N(R^{10})(R^{11})$, $-C(O)C(O)N(R^{10})(R^{11})$, $-N(R^{12})C(O)R^{13}$, $-S(O)_2R^{13}$, $-S(O)_2N(R^{10})(R^{11})$, $-S(=O)(=NH)N(R^{10})(R^{11})$, $-C(=NOR^{11})R^{13}$, $-CH_2C(O)N(R^{10})(R^{11})$, $-CH_2N(R^{12})C(O)R^{13}$, $-CH_2S(O)_2R^{13}$, and $-CH_2S(O)_2N(R^{10})(R^{11})$, wherein C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-6} cycloalkyl, $-CH_2-C_{3-6}$ cycloalkyl, C_{2-9} heterocycloalkyl, $-CH_2-C_{2-9}$ heterocycloalkyl, C_{6-10} aryl, $-CH_2-C_{6-10}$ aryl, C_{1-9} heteroaryl, $-CH_2-C_{1-9}$ heteroaryl are optionally substituted with one, two, or three groups selected from halogen, $-CN$, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{3-6} cycloalkyl, C_{2-9} heterocycloalkyl, C_{6-10} aryl, C_{1-9} heteroaryl, $-OR^{10}$, and $-N(R^{10})(R^{11})$;

each R^{10} is independently selected from hydrogen, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-6} cycloalkyl, C_{2-9} heterocycloalkyl, C_{6-10} aryl, and C_{1-9} heteroaryl, wherein C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-6} cycloalkyl, C_{2-9} heterocycloalkyl, C_{6-10} aryl, and C_{1-9} heteroaryl are optionally substituted with one, two, or three groups selected from halogen, $-CN$, hydroxy, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} alkoxy, C_{3-6} cycloalkyl, C_{2-9} heterocycloalkyl, C_{6-10} aryl, and C_{1-9} heteroaryl;

each R^{11} is independently selected from hydrogen, C_{1-6} alkyl, and C_{1-6} haloalkyl;

each R^{12} is independently selected from hydrogen, C_{1-6} alkyl, and C_{1-6} haloalkyl;

each R^{13} is independently selected C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-6} cycloalkyl, C_{2-9} heterocycloalkyl, C_{6-10} aryl, and C_{1-9} heteroaryl, wherein C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{3-6} cycloalkyl, C_{2-9} heterocycloalkyl, C_{6-10} aryl, and C_{1-9} heteroaryl are optionally substituted with one, two, or three groups selected from halogen, $-CN$, hydroxy, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} alkoxy, C_{3-6} cycloalkyl, C_{2-9} heterocycloalkyl, C_{6-10} aryl, and C_{1-9} heteroaryl; and

n is 0, 1, 2, 3, or 4.

[00100] In some embodiments is a compound of Formula (IV), or a pharmaceutically acceptable salt or solvate thereof, wherein J is S. In some embodiments is a compound of Formula (IV), or a pharmaceutically acceptable salt or solvate thereof, wherein J is O.

[00101] In some embodiments is a compound of Formula (IV), or a pharmaceutically acceptable salt or solvate thereof, wherein R^3 is selected from hydrogen, halogen, $-CN$, $-N(R^{10})(R^{11})$, C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} alkoxy, and C_{3-6} cycloalkyl, wherein C_{1-6} alkyl, C_{1-6} haloalkyl, C_{1-6} alkoxy, and C_{3-6} cycloalkyl are optionally substituted with 1-5 R^{5c} groups. In some embodiments is a compound of Formula (IV), or a pharmaceutically acceptable salt or solvate thereof, wherein R^3 is selected from hydrogen, halogen, $-CN$, C_{1-6} alkyl, C_{1-6} haloalkyl, and C_{1-6} alkoxy, wherein C_{1-6} alkyl, C_{1-6} haloalkyl, and C_{1-6} alkoxy are optionally substituted with 1-5 R^{5c} groups. In some

embodiments is a compound of Formula (IV), or a pharmaceutically acceptable salt or solvate thereof, wherein R^3 is selected from hydrogen, halogen, -CN, C_{1-6} alkyl, C_{1-6} haloalkyl, and C_{1-6} alkoxy, wherein C_{1-6} alkyl, C_{1-6} haloalkyl, and C_{1-6} alkoxy are optionally substituted with 1-3 R^{5c} groups. In some embodiments is a compound of Formula (IV), or a pharmaceutically acceptable salt or solvate thereof, wherein R^3 is selected from hydrogen, halogen, -CN, unsubstituted C_{1-6} alkyl, -CF₃, and -OCH₃. In some embodiments is a compound of Formula (IV), or a pharmaceutically acceptable salt or solvate thereof, wherein R^3 is selected from hydrogen, halogen, and -CH₃. In some embodiments is a compound of Formula (IV), or a pharmaceutically acceptable salt or solvate thereof, wherein R^3 is hydrogen.

[00102] In some embodiments is a compound of Formula (IV), or a pharmaceutically acceptable salt or solvate thereof, wherein each R^2 is independently selected from -OR¹⁰, C_{1-6} alkyl, and C_{1-6} haloalkyl, wherein C_{1-6} alkyl and C_{1-6} haloalkyl are optionally substituted with 1-5 R^{5b} groups. In some embodiments is a compound of Formula (IV), or a pharmaceutically acceptable salt or solvate thereof, wherein each R^2 is independently selected from C_{1-6} alkyl optionally substituted with 1-5 R^{5b} groups. In some embodiments is a compound of Formula (IV), or a pharmaceutically acceptable salt or solvate thereof, wherein each R^2 is independently selected from C_{1-6} alkyl optionally substituted with -OH. In some embodiments is a compound of Formula (IV), or a pharmaceutically acceptable salt or solvate thereof, wherein each R^2 is -CH₂OH. In some embodiments is a compound of Formula (IV), or a pharmaceutically acceptable salt or solvate thereof, wherein each R^2 is independently selected from unsubstituted C_{1-6} alkyl. In some embodiments is a compound of Formula (IV), or a pharmaceutically acceptable salt or solvate thereof, wherein each R^2 is -CH₃. In some embodiments is a compound of Formula (IV), or a pharmaceutically acceptable salt or solvate thereof, wherein each R^2 is -CH₂CH₃. In some embodiments is a compound of Formula (IV), or a pharmaceutically acceptable salt or solvate thereof, wherein each R^2 is -CH(CH₃)₂. In some embodiments is a compound of Formula (IV), or a pharmaceutically acceptable salt or solvate thereof, wherein each R^2 is independently selected from -OR¹⁰, wherein R^{10} is C_{1-6} alkyl. In some embodiments is a compound of Formula (IV), or a pharmaceutically acceptable salt or solvate thereof, wherein each R^2 is -OCH₃.

[00103] In some embodiments is a compound of Formula (IV), or a pharmaceutically acceptable salt or solvate thereof, wherein n is 1. In some embodiments is a compound of Formula (IV), or a pharmaceutically acceptable salt or solvate thereof, wherein n is 2. In some embodiments is a compound of Formula (IV), or a pharmaceutically acceptable salt or solvate thereof, wherein n is 3. In some embodiments is a compound of Formula (IV), or a pharmaceutically acceptable salt or

solvate thereof, wherein n is 4. In some embodiments is a compound of Formula (IV), or a pharmaceutically acceptable salt or solvate thereof, wherein n is 0.

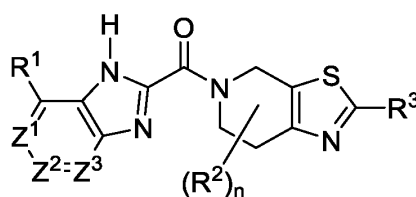
[00104] In some embodiments is a compound of Formula (IV), or a pharmaceutically acceptable salt or solvate thereof, wherein R^1 is selected from halogen, -CN, -OR¹⁰, C₁₋₆alkyl, C₁₋₆haloalkyl, C₆₋₁₀aryl, and C₁₋₉heteroaryl, wherein C₁₋₆alkyl and C₁₋₆haloalkyl are optionally substituted with 1-5 R^{5a} groups. In some embodiments is a compound of Formula (IV), or a pharmaceutically acceptable salt or solvate thereof, wherein R^1 is selected from halogen, -CN, -OR¹⁰, C₁₋₆alkyl, and C₁₋₆haloalkyl wherein C₁₋₆alkyl and C₁₋₆haloalkyl are optionally substituted with 1-5 R^{5a} groups. In some embodiments is a compound of Formula (IV), or a pharmaceutically acceptable salt or solvate thereof, wherein R^1 is selected from halogen, -CN, -OR¹⁰, unsubstituted C₁₋₆alkyl, and unsubstituted C₁₋₆haloalkyl. In some embodiments is a compound of Formula (IV), or a pharmaceutically acceptable salt or solvate thereof, wherein R^1 is halogen. In some embodiments is a compound of Formula (IV), or a pharmaceutically acceptable salt or solvate thereof, wherein R^1 is -CN. In some embodiments is a compound of Formula (IV), or a pharmaceutically acceptable salt or solvate thereof, wherein R^1 is -OR¹⁰. In some embodiments is a compound of Formula (IV), or a pharmaceutically acceptable salt or solvate thereof, wherein R^1 is -OR¹⁰, wherein R¹⁰ is hydrogen C₁₋₆alkyl. In some embodiments is a compound of Formula (IV), or a pharmaceutically acceptable salt or solvate thereof, wherein R^1 is -OH. In some embodiments is a compound of Formula (IV), or a pharmaceutically acceptable salt or solvate thereof, wherein R^1 is -OCH₃. In some embodiments is a compound of Formula (IV), or a pharmaceutically acceptable salt or solvate thereof, wherein R^1 is unsubstituted C₁₋₆alkyl. In some embodiments is a compound of Formula (IV), or a pharmaceutically acceptable salt or solvate thereof, wherein R^1 is -CH₃. In some embodiments is a compound of Formula (IV), or a pharmaceutically acceptable salt or solvate thereof, wherein R^1 is unsubstituted C₁₋₆haloalkyl. In some embodiments is a compound of Formula (IV), or a pharmaceutically acceptable salt or solvate thereof, wherein R^1 is -CF₃. In some embodiments is a compound of Formula (IV), or a pharmaceutically acceptable salt or solvate thereof, wherein R^1 is selected from halogen, -CN, -OH, -OCH₃, -CH₃, and -CF₃.

[00105] In some embodiments is a compound of Formula (IV), or a pharmaceutically acceptable salt or solvate thereof, wherein Z¹, Z², and Z³ are each independently C(R⁴). In some embodiments is a compound of Formula (IV), or a pharmaceutically acceptable salt or solvate thereof, wherein Z¹ and Z² are C(R⁴) and Z³ is N. In some embodiments is a compound of Formula (IV), or a pharmaceutically acceptable salt or solvate thereof, wherein Z¹ and Z³ are N and Z² is C(R⁴). In some embodiments is a compound of Formula (IV), or a pharmaceutically

acceptable salt or solvate thereof, wherein Z^1 and Z^3 are $C(R^4)$ and Z^2 is N. In some embodiments is a compound of Formula (IV), or a pharmaceutically acceptable salt or solvate thereof, wherein Z^2 and Z^3 are $C(R^4)$ and Z^1 is N.

[00106] In some embodiments is a compound of Formula (IV), or a pharmaceutically acceptable salt or solvate thereof, wherein each R^4 is independently selected from hydrogen, halogen, -CN, -OR¹⁰, C₁₋₆alkyl, C₁₋₆haloalkyl, and C₃₋₆cycloalkyl, wherein C₁₋₆alkyl, C₁₋₆haloalkyl, and C₃₋₆cycloalkyl are optionally substituted with 1-5 R^{5d} groups. In some embodiments is a compound of Formula (IV), or a pharmaceutically acceptable salt or solvate thereof, wherein each R^4 is independently selected from hydrogen, halogen, and unsubstituted C₁₋₆alkyl. In some embodiments is a compound of Formula (IV), or a pharmaceutically acceptable salt or solvate thereof, wherein each R^4 is independently selected from hydrogen and halogen. In some embodiments is a compound of Formula (IV), or a pharmaceutically acceptable salt or solvate thereof, wherein each R^4 is hydrogen.

[00107] In some embodiments, described herein is a compound of Formula (IVa), or a pharmaceutically acceptable salt or solvate thereof:



Formula (IVa);

wherein,

Z^1 , Z^2 , and Z^3 are each independently $C(R^4)$ or N, wherein at least one of Z^1 , Z^2 , and Z^3 is $C(R^4)$;

R^1 is selected from hydrogen, halogen, -CN, -OR¹⁰, -SR¹⁰, -N(R¹⁰)(R¹¹), C₁₋₆alkyl, C₁₋₆haloalkyl, C₂₋₆alkenyl, C₂₋₆alkynyl, C₃₋₆cycloalkyl, C₂₋₉heterocycloalkyl, C₆₋₁₀aryl, and C₁₋₉heteroaryl, wherein C₁₋₆alkyl, C₁₋₆haloalkyl, C₂₋₆alkenyl, C₂₋₆alkynyl, C₃₋₆cycloalkyl, C₂₋₉heterocycloalkyl, C₆₋₁₀aryl, and C₁₋₉heteroaryl are optionally substituted with 1-5 R^{5a} groups;

each R^2 is independently selected from halogen, -CN, -OR¹⁰, -SR¹⁰, -N(R¹⁰)(R¹¹), C₁₋₆alkyl, C₁₋₆haloalkyl, C₂₋₆alkenyl, C₂₋₆alkynyl, C₃₋₆cycloalkyl, C₂₋₉heterocycloalkyl, C₆₋₁₀aryl, and C₁₋₉heteroaryl, wherein C₁₋₆alkyl, C₁₋₆haloalkyl, C₂₋₆alkenyl, C₂₋₆alkynyl, C₃₋₆cycloalkyl, C₂₋₉heterocycloalkyl, C₆₋₁₀aryl, and C₁₋₉heteroaryl are optionally substituted with 1-5 R^{5b} groups;

R³ is selected from hydrogen, halogen, -CN, -SR¹⁰, -N(R¹⁰)(R¹¹), C₁₋₆alkyl, C₁₋₆haloalkyl, C₁₋₆alkoxy, C₂₋₆alkenyl, C₂₋₆alkynyl, C₃₋₆cycloalkyl, C₂₋₉heterocycloalkyl, C₆₋₁₀aryl, and C₁₋₉heteroaryl, wherein C₁₋₆alkyl, C₁₋₆haloalkyl, C₁₋₆alkoxy, C₂₋₆alkenyl, C₂₋₆alkynyl, C₃₋₆cycloalkyl, C₂₋₉heterocycloalkyl, C₆₋₁₀aryl, and C₁₋₉heteroaryl are optionally substituted with 1-5 R^{5c} groups;

each R⁴ is independently selected from hydrogen, halogen, -CN, -OR¹⁰, -SR¹⁰, -N(R¹⁰)(R¹¹), C₁₋₆alkyl, C₁₋₆haloalkyl, C₂₋₆alkenyl, C₂₋₆alkynyl, C₃₋₆cycloalkyl, C₂₋₉heterocycloalkyl, C₆₋₁₀aryl, and C₁₋₉heteroaryl, wherein C₁₋₆alkyl, C₁₋₆haloalkyl, C₂₋₆alkenyl, C₂₋₆alkynyl, C₃₋₆cycloalkyl, C₂₋₉heterocycloalkyl, C₆₋₁₀aryl, and C₁₋₉heteroaryl are optionally substituted with 1-5 R^{5d} groups;

each R^{5a}, R^{5b}, R^{5c}, and R^{5d} is each independently selected from halogen, oxo, -CN, C₁₋₆alkyl, C₁₋₆haloalkyl, C₂₋₆alkenyl, C₂₋₆alkynyl, C₃₋₆cycloalkyl, -CH₂-C₃₋₆cycloalkyl, C₂₋₉heterocycloalkyl, -CH₂-C₂₋₉heterocycloalkyl, C₆₋₁₀aryl, -CH₂-C₆₋₁₀aryl, C₁₋₉heteroaryl, -CH₂-C₁₋₉heteroaryl, -OR¹⁰, -SR¹⁰, -N(R¹⁰)(R¹¹), -C(O)OR¹⁰, -OC(O)N(R¹⁰)(R¹¹), -N(R¹²)C(O)N(R¹⁰)(R¹¹), -N(R¹²)C(O)OR¹³, -N(R¹²)S(O)₂R¹³, -C(O)R¹³, -S(O)R¹³, -OC(O)R¹³, -C(O)N(R¹⁰)(R¹¹), -C(O)C(O)N(R¹⁰)(R¹¹), -N(R¹²)C(O)R¹³, -S(O)₂R¹³, -S(O)₂N(R¹⁰)(R¹¹), -S(=O)(=NH)N(R¹⁰)(R¹¹), -C(=NOR¹¹)R¹³, -CH₂C(O)N(R¹⁰)(R¹¹), -CH₂N(R¹²)C(O)R¹³, -CH₂S(O)₂R¹³, and -CH₂S(O)₂N(R¹⁰)(R¹¹), wherein C₁₋₆alkyl, C₁₋₆haloalkyl, C₂₋₆alkenyl, C₂₋₆alkynyl, C₃₋₆cycloalkyl, -CH₂-C₃₋₆cycloalkyl, C₂₋₉heterocycloalkyl, -CH₂-C₂₋₉heterocycloalkyl, C₆₋₁₀aryl, -CH₂-C₆₋₁₀aryl, C₁₋₉heteroaryl, -CH₂-C₁₋₉heteroaryl are optionally substituted with one, two, or three groups selected from halogen, -CN, C₁₋₆alkyl, C₁₋₆haloalkyl, C₃₋₆cycloalkyl, C₂₋₉heterocycloalkyl, C₆₋₁₀aryl, C₁₋₉heteroaryl, -OR¹⁰, and -N(R¹⁰)(R¹¹);

each R¹⁰ is independently selected from hydrogen, C₁₋₆alkyl, C₁₋₆haloalkyl, C₂₋₆alkenyl, C₂₋₆alkynyl, C₃₋₆cycloalkyl, C₂₋₉heterocycloalkyl, C₆₋₁₀aryl, and C₁₋₉heteroaryl, wherein C₁₋₆alkyl, C₂₋₆alkenyl, C₂₋₆alkynyl, C₃₋₆cycloalkyl, C₂₋₉heterocycloalkyl, C₆₋₁₀aryl, and C₁₋₉heteroaryl are optionally substituted with one, two, or three groups selected from halogen, -CN, hydroxy, C₁₋₆alkyl, C₁₋₆haloalkyl, C₁₋₆alkoxy, C₃₋₆cycloalkyl, C₂₋₉heterocycloalkyl, C₆₋₁₀aryl, and C₁₋₉heteroaryl;

each R¹¹ is independently selected from hydrogen, C₁₋₆alkyl, and C₁₋₆haloalkyl;

each R¹² is independently selected from hydrogen, C₁₋₆alkyl, and C₁₋₆haloalkyl;

each R¹³ is independently selected C₁₋₆alkyl, C₂₋₆alkenyl, C₂₋₆alkynyl, C₃₋₆cycloalkyl, C₂₋₉heterocycloalkyl, C₆₋₁₀aryl, and C₁₋₉heteroaryl, wherein C₁₋₆alkyl, C₂₋₆alkenyl, C₂₋₆alkynyl, C₃₋₆cycloalkyl, C₂₋₉heterocycloalkyl, C₆₋₁₀aryl, and C₁₋₉heteroaryl are optionally

substituted with one, two, or three groups selected from halogen, -CN, hydroxy, C₁₋₆alkyl, C₁₋₆haloalkyl, C₁₋₆alkoxy, C₃₋₆cycloalkyl, C₂₋₉heterocycloalkyl, C₆₋₁₀aryl, and C₁₋₉heteroaryl; and
n is 0, 1, 2, 3, or 4.

[00108] In some embodiments is a compound of Formula (IVa), or a pharmaceutically acceptable salt or solvate thereof, wherein R³ is selected from hydrogen, halogen, -CN, -N(R¹⁰)(R¹¹), C₁₋₆alkyl, C₁₋₆haloalkyl, C₁₋₆alkoxy, and C₃₋₆cycloalkyl, wherein C₁₋₆alkyl, C₁₋₆haloalkyl, C₁₋₆alkoxy, and C₃₋₆cycloalkyl are optionally substituted with 1-5 R^{5c} groups. In some embodiments is a compound of Formula (IVa), or a pharmaceutically acceptable salt or solvate thereof, wherein R³ is selected from hydrogen, halogen, -CN, C₁₋₆alkyl, C₁₋₆haloalkyl, and C₁₋₆alkoxy, wherein C₁₋₆alkyl, C₁₋₆haloalkyl, and C₁₋₆alkoxy are optionally substituted with 1-5 R^{5c} groups. In some embodiments is a compound of Formula (IVa), or a pharmaceutically acceptable salt or solvate thereof, wherein R³ is selected from hydrogen, halogen, -CN, C₁₋₆alkyl, C₁₋₆haloalkyl, and C₁₋₆alkoxy, wherein C₁₋₆alkyl, C₁₋₆haloalkyl, and C₁₋₆alkoxy are optionally substituted with 1-3 R^{5c} groups. In some embodiments is a compound of Formula (IVa), or a pharmaceutically acceptable salt or solvate thereof, wherein R³ is selected from hydrogen, halogen, -CN, unsubstituted C₁₋₆alkyl, -CF₃, and -OCH₃. In some embodiments is a compound of Formula (IVa), or a pharmaceutically acceptable salt or solvate thereof, wherein R³ is selected from hydrogen, halogen, and -CH₃. In some embodiments is a compound of Formula (IVa), or a pharmaceutically acceptable salt or solvate thereof, wherein R³ is hydrogen.

[00109] In some embodiments is a compound of Formula (IVa), or a pharmaceutically acceptable salt or solvate thereof, wherein each R² is independently selected from -OR¹⁰, C₁₋₆alkyl, and C₁₋₆haloalkyl, wherein C₁₋₆alkyl and C₁₋₆haloalkyl are optionally substituted with 1-5 R^{5b} groups. In some embodiments is a compound of Formula (IVa), or a pharmaceutically acceptable salt or solvate thereof, wherein each R² is independently selected from C₁₋₆alkyl optionally substituted with 1-5 R^{5b} groups. In some embodiments is a compound of Formula (IVa), or a pharmaceutically acceptable salt or solvate thereof, wherein each R² is independently selected from C₁₋₆alkyl optionally substituted with -OH. In some embodiments is a compound of Formula (IVa), or a pharmaceutically acceptable salt or solvate thereof, wherein each R² is -CH₂OH. In some embodiments is a compound of Formula (IVa), or a pharmaceutically acceptable salt or solvate thereof, wherein each R² is independently selected from unsubstituted C₁₋₆alkyl. In some embodiments is a compound of Formula (IVa), or a pharmaceutically acceptable salt or solvate thereof, wherein each R² is -CH₃. In some embodiments is a compound of Formula (IVa), or a pharmaceutically acceptable salt or solvate thereof, wherein each R² is -

CH₂CH₃. In some embodiments is a compound of Formula (IVa), or a pharmaceutically acceptable salt or solvate thereof, wherein each R² is -CH(CH₃)₂. In some embodiments is a compound of Formula (IVa), or a pharmaceutically acceptable salt or solvate thereof, wherein each R² is independently selected from -OR¹⁰, wherein R¹⁰ is C₁₋₆alkyl. In some embodiments is a compound of Formula (IVa), or a pharmaceutically acceptable salt or solvate thereof, wherein each R² is -OCH₃.

[00110] In some embodiments is a compound of Formula (IVa), or a pharmaceutically acceptable salt or solvate thereof, wherein n is 1. In some embodiments is a compound of Formula (IVa), or a pharmaceutically acceptable salt or solvate thereof, wherein n is 2. In some embodiments is a compound of Formula (IVa), or a pharmaceutically acceptable salt or solvate thereof, wherein n is 3. In some embodiments is a compound of Formula (IVa), or a pharmaceutically acceptable salt or solvate thereof, wherein n is 4. In some embodiments is a compound of Formula (IVa), or a pharmaceutically acceptable salt or solvate thereof, wherein n is 0.

[00111] In some embodiments is a compound of Formula (IVa), or a pharmaceutically acceptable salt or solvate thereof, wherein R¹ is selected from halogen, -CN, -OR¹⁰, C₁₋₆alkyl, C₁₋₆haloalkyl, C₆₋₁₀aryl, and C₁₋₉heteroaryl, wherein C₁₋₆alkyl and C₁₋₆haloalkyl are optionally substituted with 1-5 R^{5a} groups. In some embodiments is a compound of Formula (IVa), or a pharmaceutically acceptable salt or solvate thereof, wherein R¹ is selected from halogen, -CN, -OR¹⁰, C₁₋₆alkyl, and C₁₋₆haloalkyl wherein C₁₋₆alkyl and C₁₋₆haloalkyl are optionally substituted with 1-5 R^{5a} groups. In some embodiments is a compound of Formula (IVa), or a pharmaceutically acceptable salt or solvate thereof, wherein R¹ is selected from halogen, -CN, -OR¹⁰, unsubstituted C₁₋₆alkyl, and unsubstituted C₁₋₆haloalkyl. In some embodiments is a compound of Formula (IVa), or a pharmaceutically acceptable salt or solvate thereof, wherein R¹ is halogen. In some embodiments is a compound of Formula (IVa), or a pharmaceutically acceptable salt or solvate thereof, wherein R¹ is -CN. In some embodiments is a compound of Formula (IVa), or a pharmaceutically acceptable salt or solvate thereof, wherein R¹ is -OR¹⁰. In some embodiments is a compound of Formula (IVa), or a pharmaceutically acceptable salt or solvate thereof, wherein R¹ is -OR¹⁰, wherein R¹⁰ is hydrogen C₁₋₆alkyl. In some embodiments is a compound of Formula (IVa), or a pharmaceutically acceptable salt or solvate thereof, wherein R¹ is -OH. In some embodiments is a compound of Formula (IVa), or a pharmaceutically acceptable salt or solvate thereof, wherein R¹ is -OCH₃. In some embodiments is a compound of Formula (IVa), or a pharmaceutically acceptable salt or solvate thereof, wherein R¹ is unsubstituted C₁₋₆alkyl. In some embodiments is a compound of Formula (IVa), or a

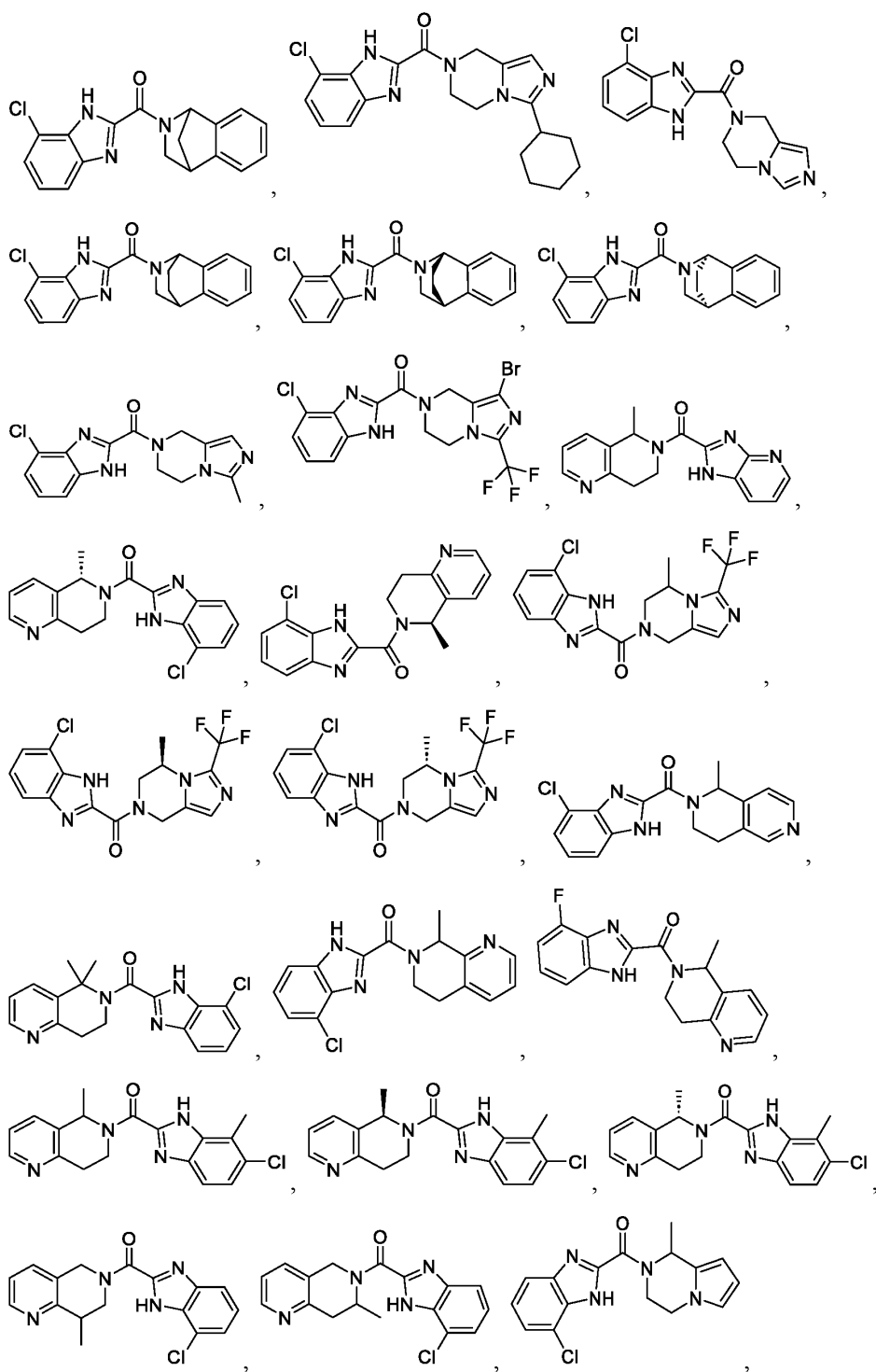
pharmaceutically acceptable salt or solvate thereof, wherein R^1 is $-CH_3$. In some embodiments is a compound of Formula (IVa), or a pharmaceutically acceptable salt or solvate thereof, wherein R^1 is unsubstituted C_{1-6} haloalkyl. In some embodiments is a compound of Formula (IVa), or a pharmaceutically acceptable salt or solvate thereof, wherein R^1 is $-CF_3$. In some embodiments is a compound of Formula (IVa), or a pharmaceutically acceptable salt or solvate thereof, wherein R^1 is selected from halogen, $-CN$, $-OH$, $-OCH_3$, $-CH_3$, and $-CF_3$.

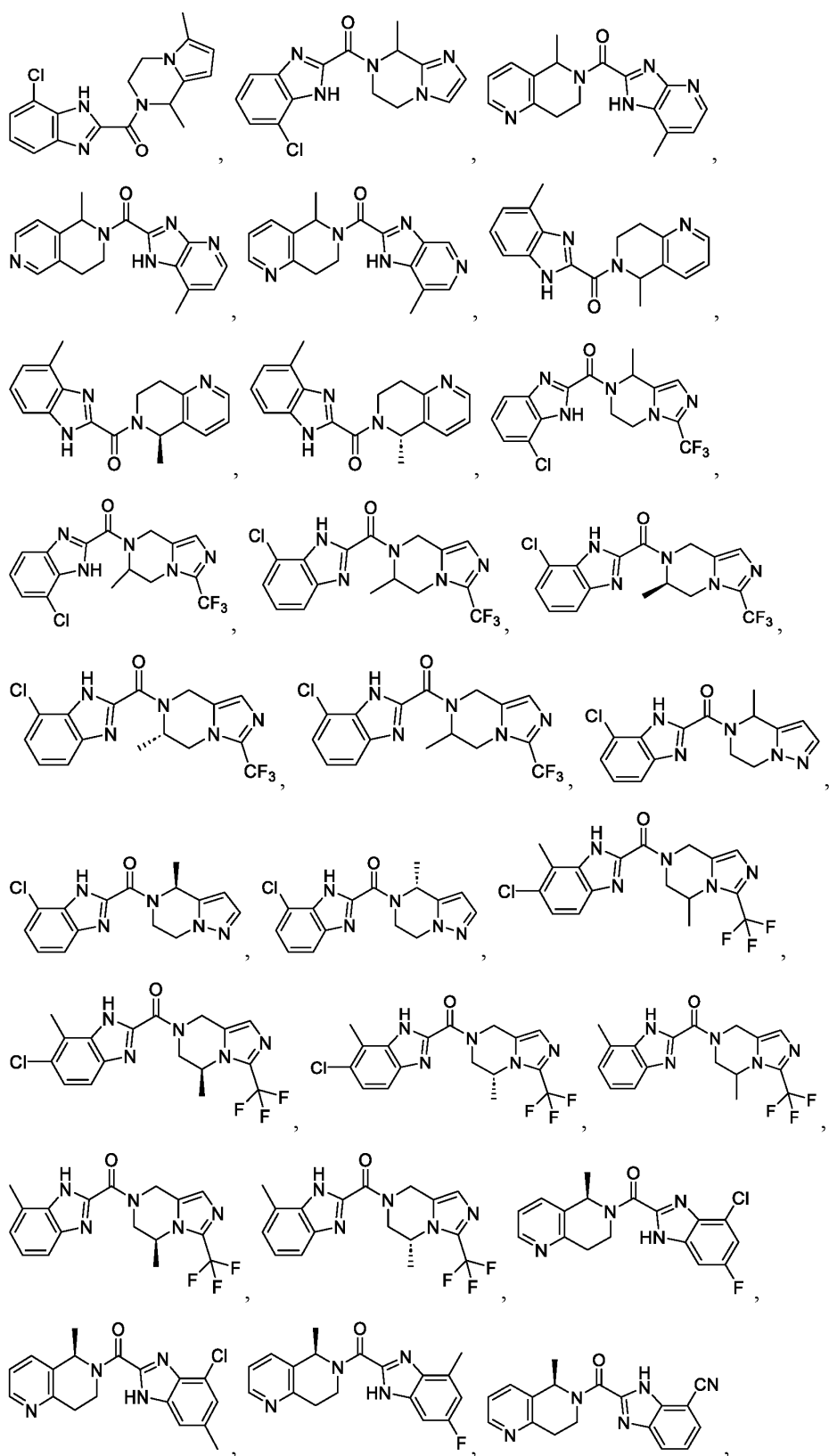
[00112] In some embodiments is a compound of Formula (IVa), or a pharmaceutically acceptable salt or solvate thereof, wherein Z^1 , Z^2 , and Z^3 are each independently $C(R^4)$. In some embodiments is a compound of Formula (IVa), or a pharmaceutically acceptable salt or solvate thereof, wherein Z^1 and Z^2 are $C(R^4)$ and Z^3 is N. In some embodiments is a compound of Formula (IVa), or a pharmaceutically acceptable salt or solvate thereof, wherein Z^1 and Z^3 are N and Z^2 is $C(R^4)$. In some embodiments is a compound of Formula (IVa), or a pharmaceutically acceptable salt or solvate thereof, wherein Z^1 and Z^3 are $C(R^4)$ and Z^2 is N. In some embodiments is a compound of Formula (IVa), or a pharmaceutically acceptable salt or solvate thereof, wherein Z^2 and Z^3 are $C(R^4)$ and Z^1 is N.

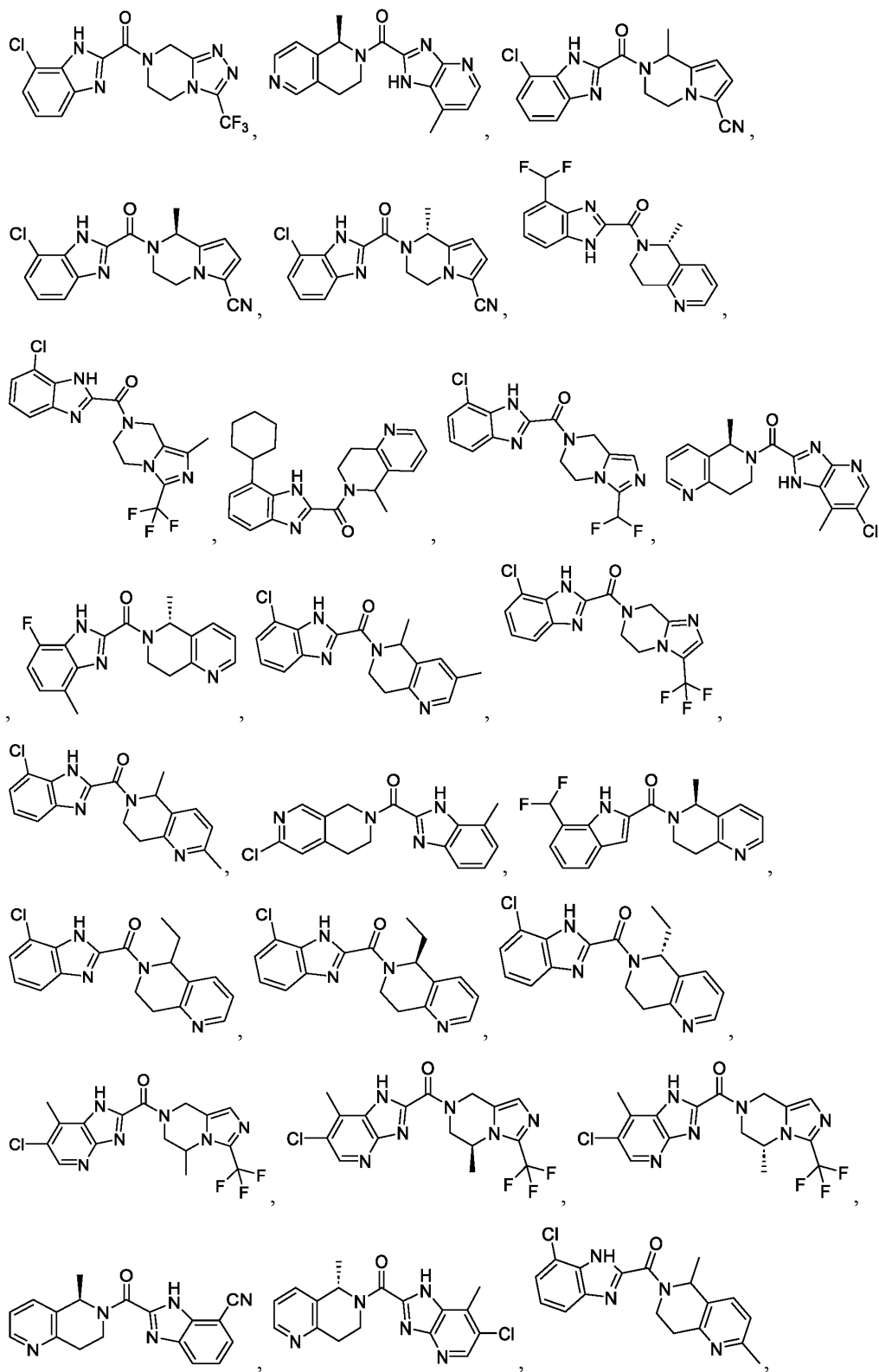
[00113] In some embodiments is a compound of Formula (IVa), or a pharmaceutically acceptable salt or solvate thereof, wherein each R^4 is independently selected from hydrogen, halogen, $-CN$, $-OR^{10}$, C_{1-6} alkyl, C_{1-6} haloalkyl, and C_{3-6} cycloalkyl, wherein C_{1-6} alkyl, C_{1-6} haloalkyl, and C_{3-6} cycloalkyl are optionally substituted with 1-5 R^{5d} groups. In some embodiments is a compound of Formula (IVa), or a pharmaceutically acceptable salt or solvate thereof, wherein each R^4 is independently selected from hydrogen, halogen, and unsubstituted C_{1-6} alkyl. In some embodiments is a compound of Formula (IVa), or a pharmaceutically acceptable salt or solvate thereof, wherein each R^4 is independently selected from hydrogen and halogen. In some embodiments is a compound of Formula (IVa), or a pharmaceutically acceptable salt or solvate thereof, wherein each R^4 is hydrogen.

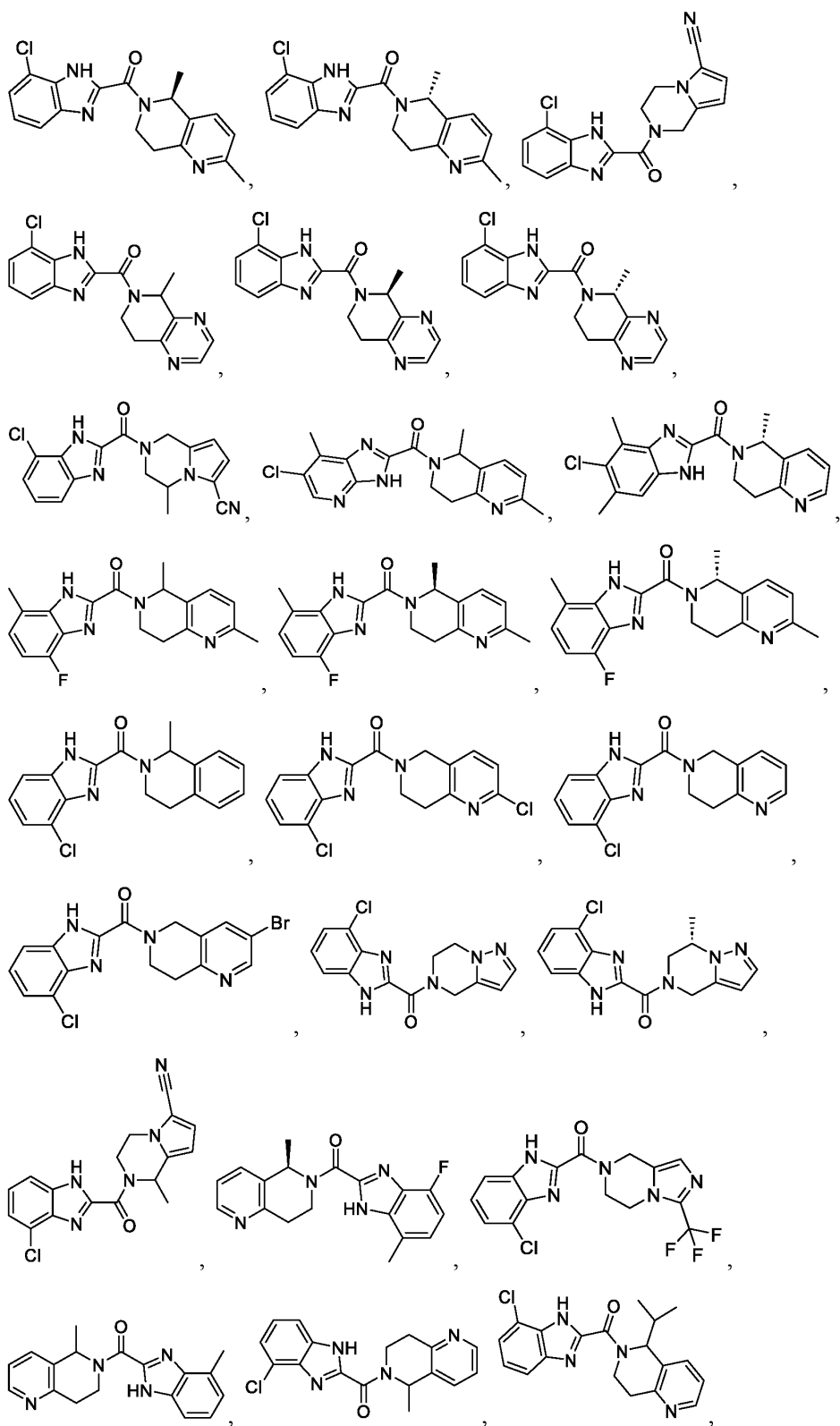
[00114] Any combination of the groups described above for the various variables is contemplated herein. Throughout the specification, groups and substituents thereof are chosen by one skilled in the field to provide stable moieties and compounds.

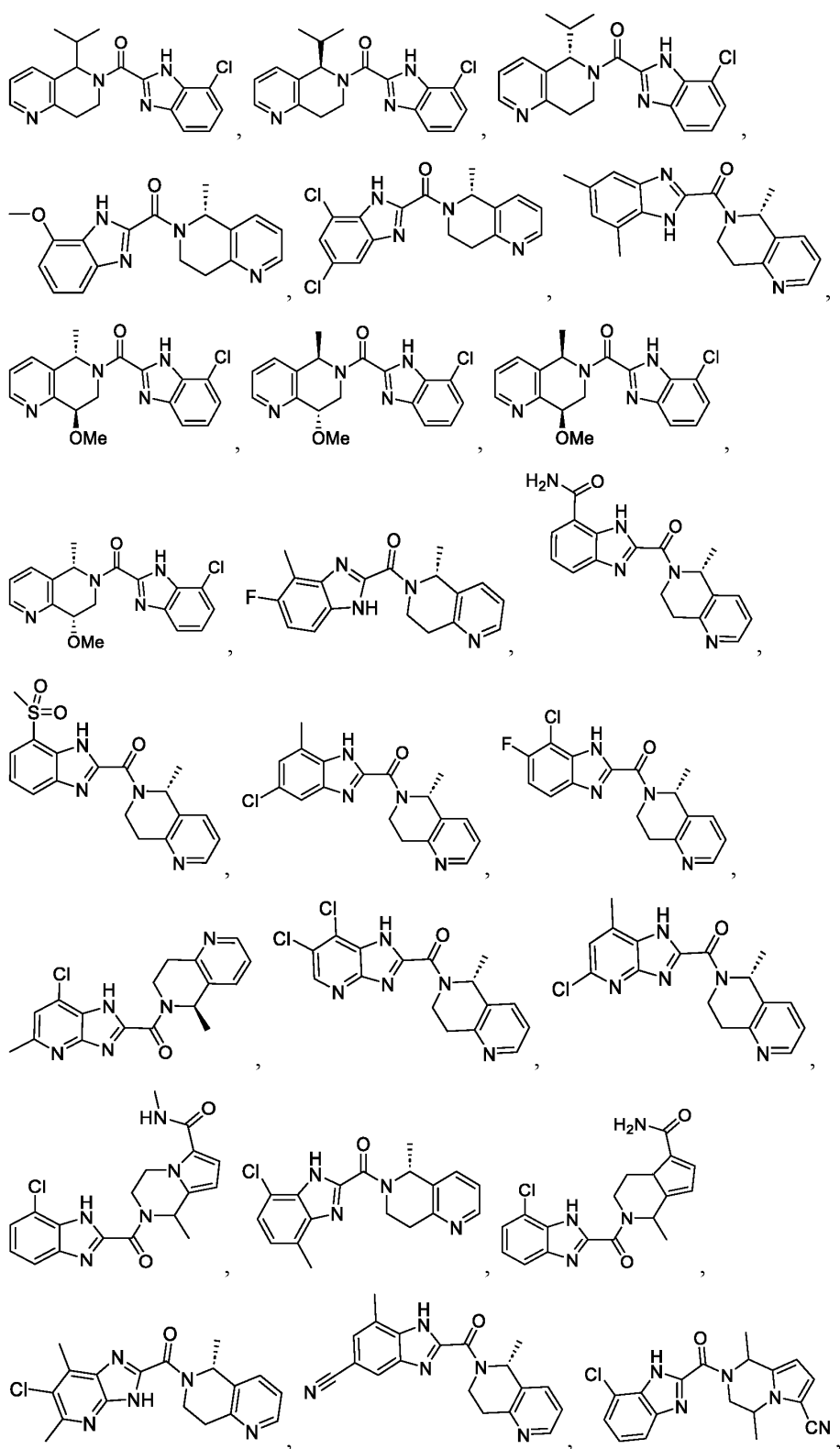
[00115] In some embodiments is a compound, or a pharmaceutically acceptable salt or solvate thereof, selected from:

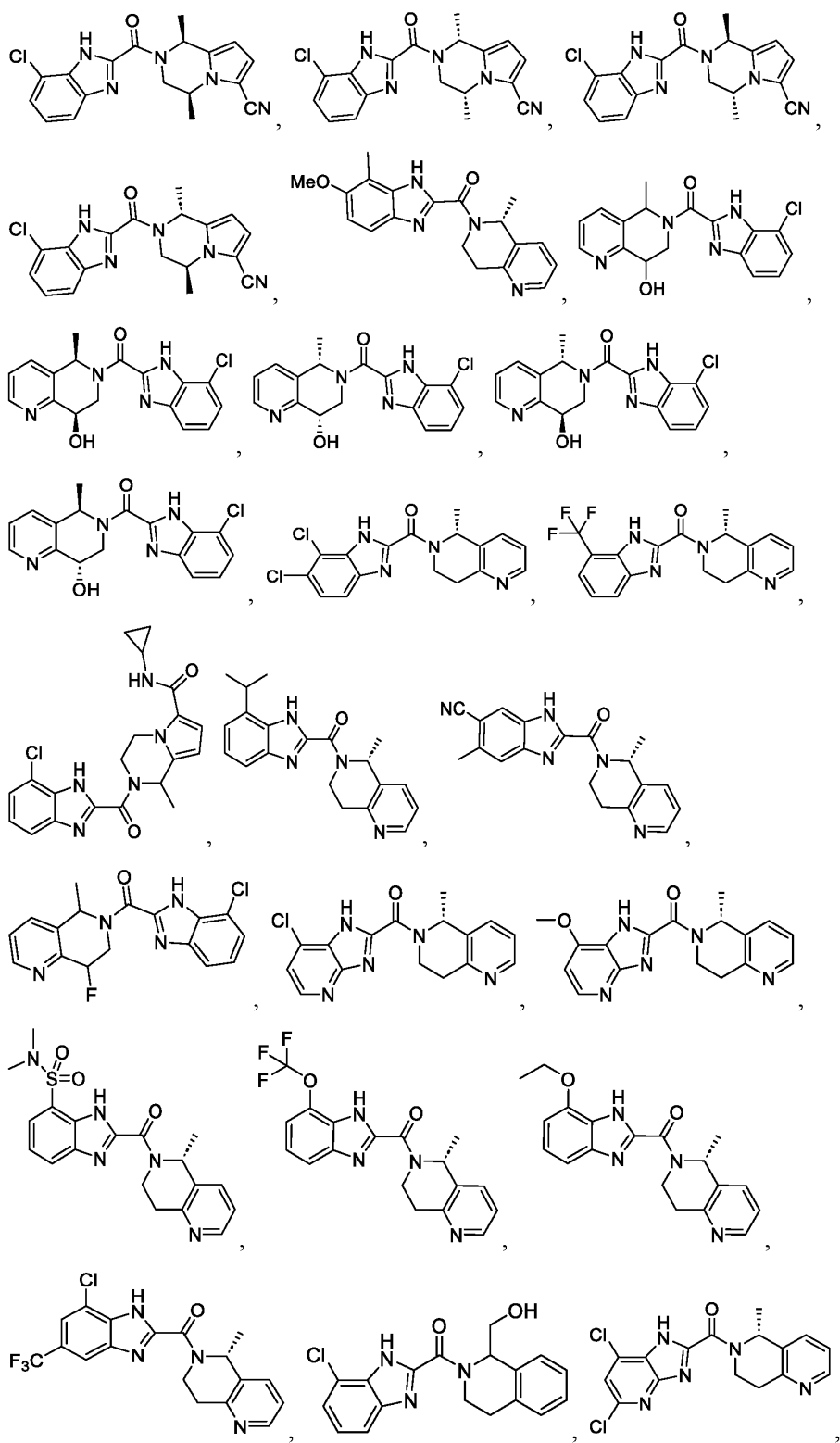


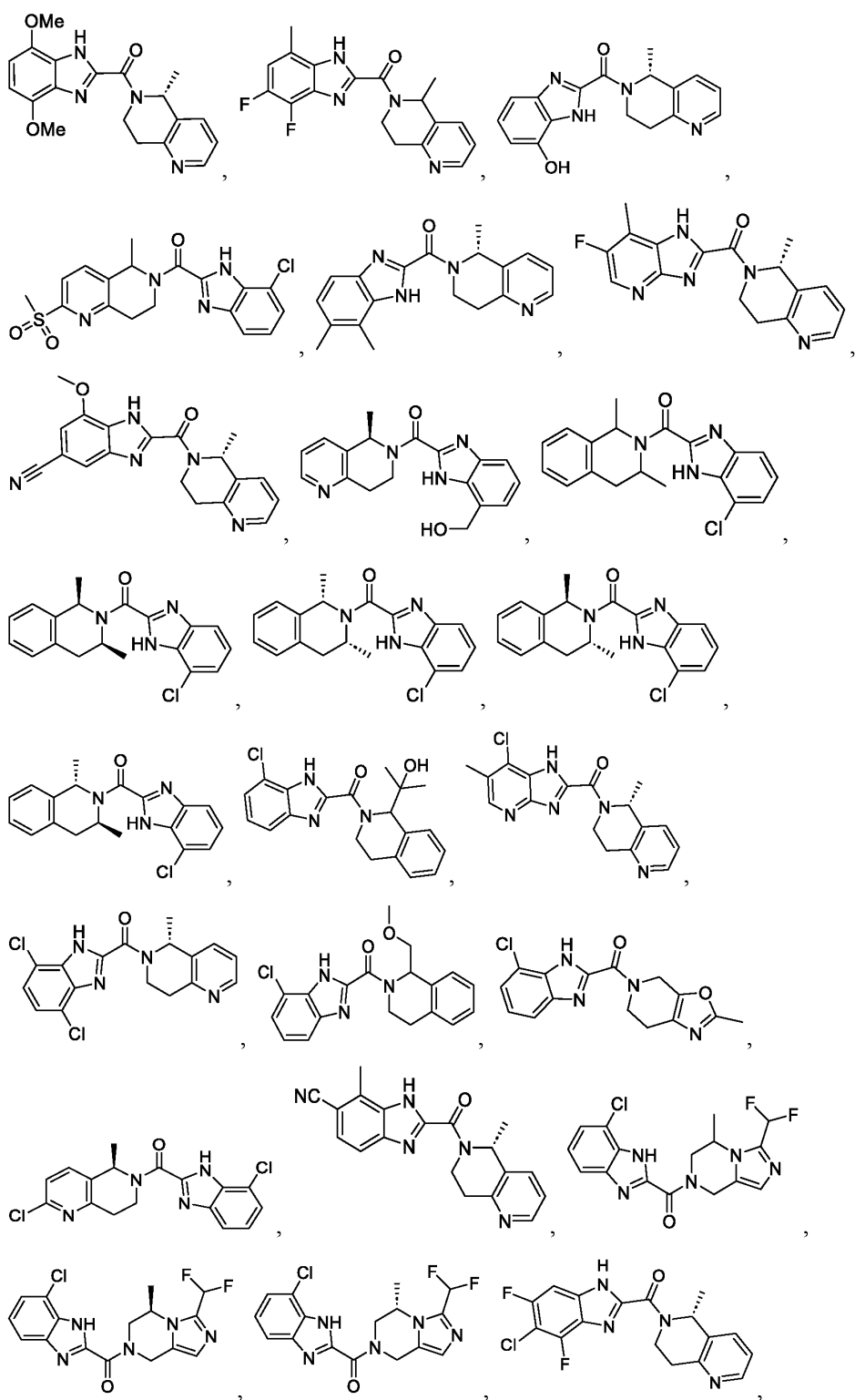


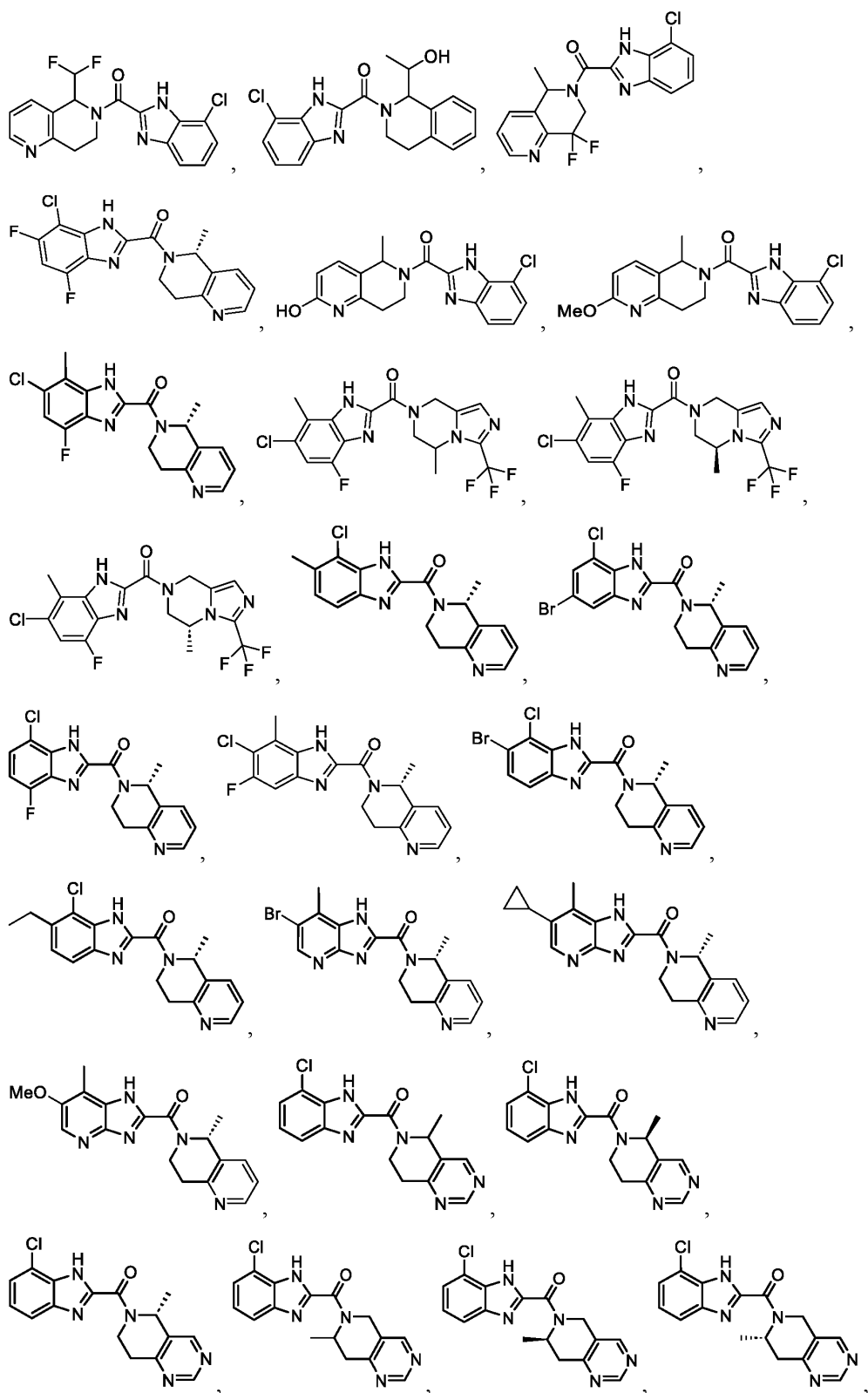


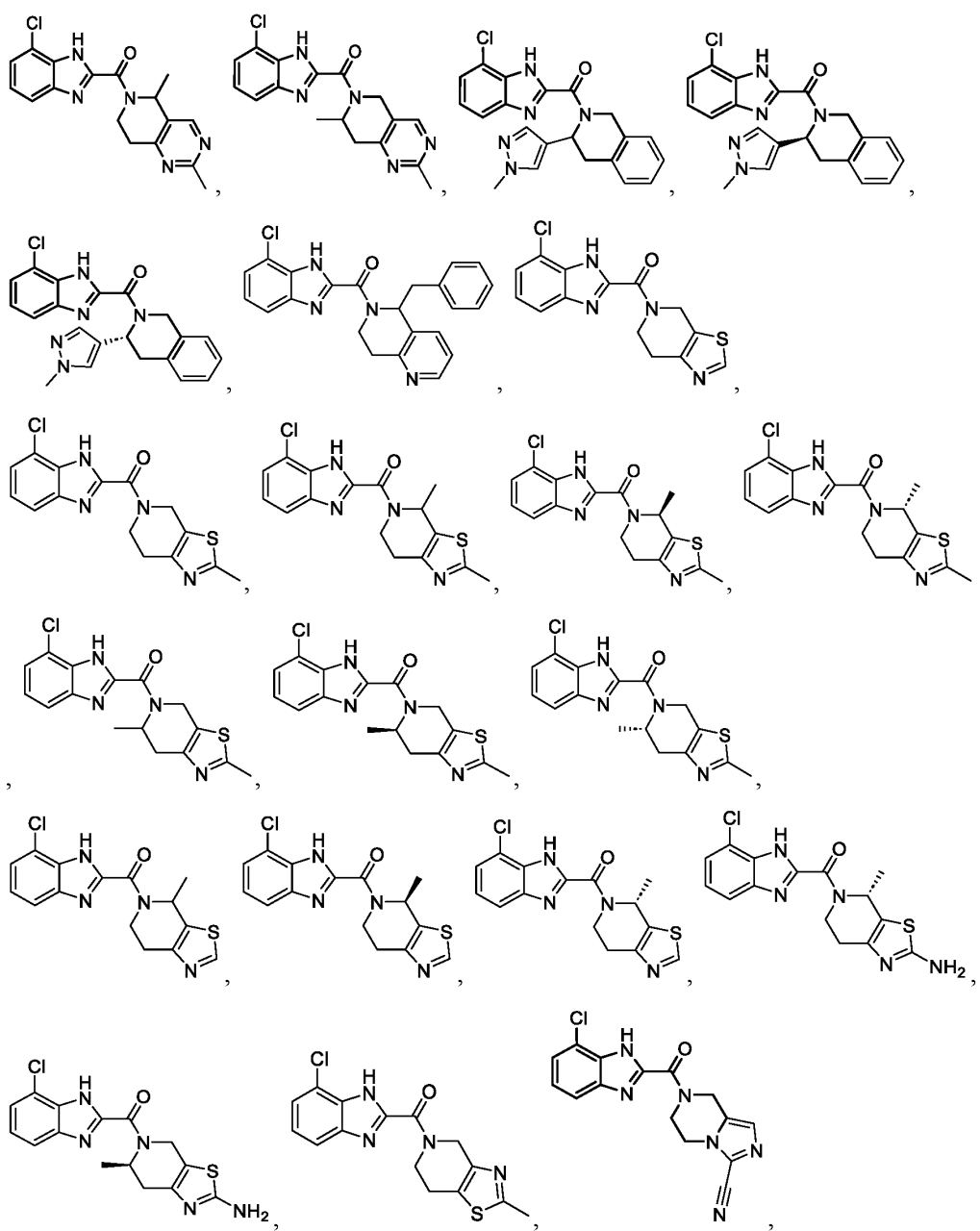


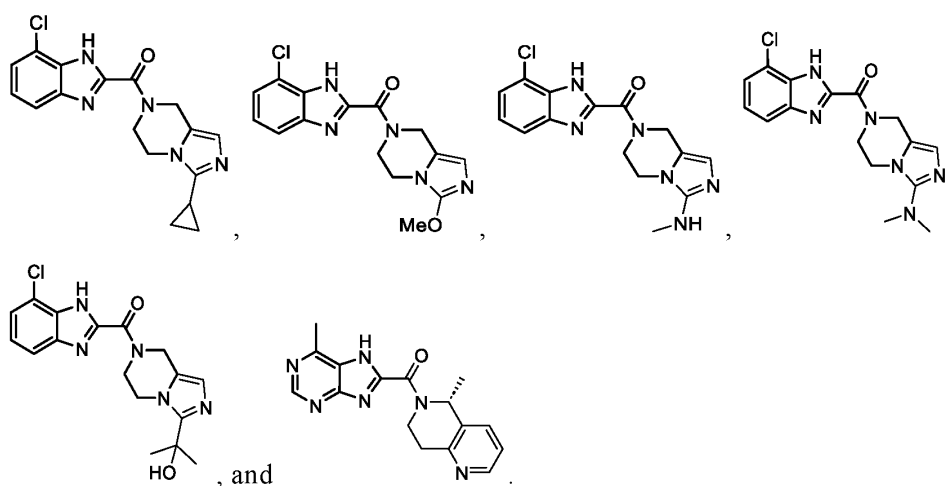




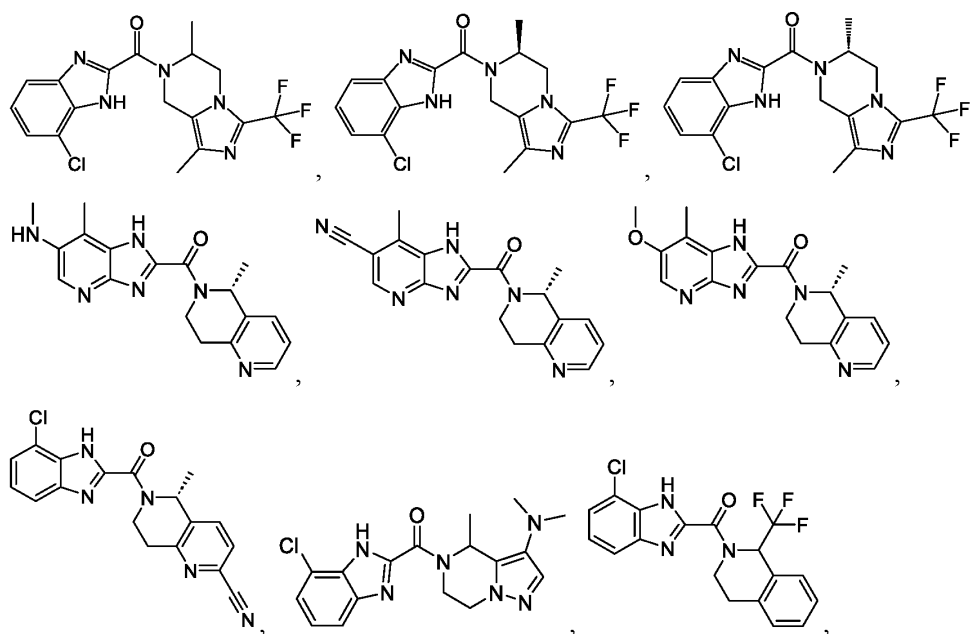


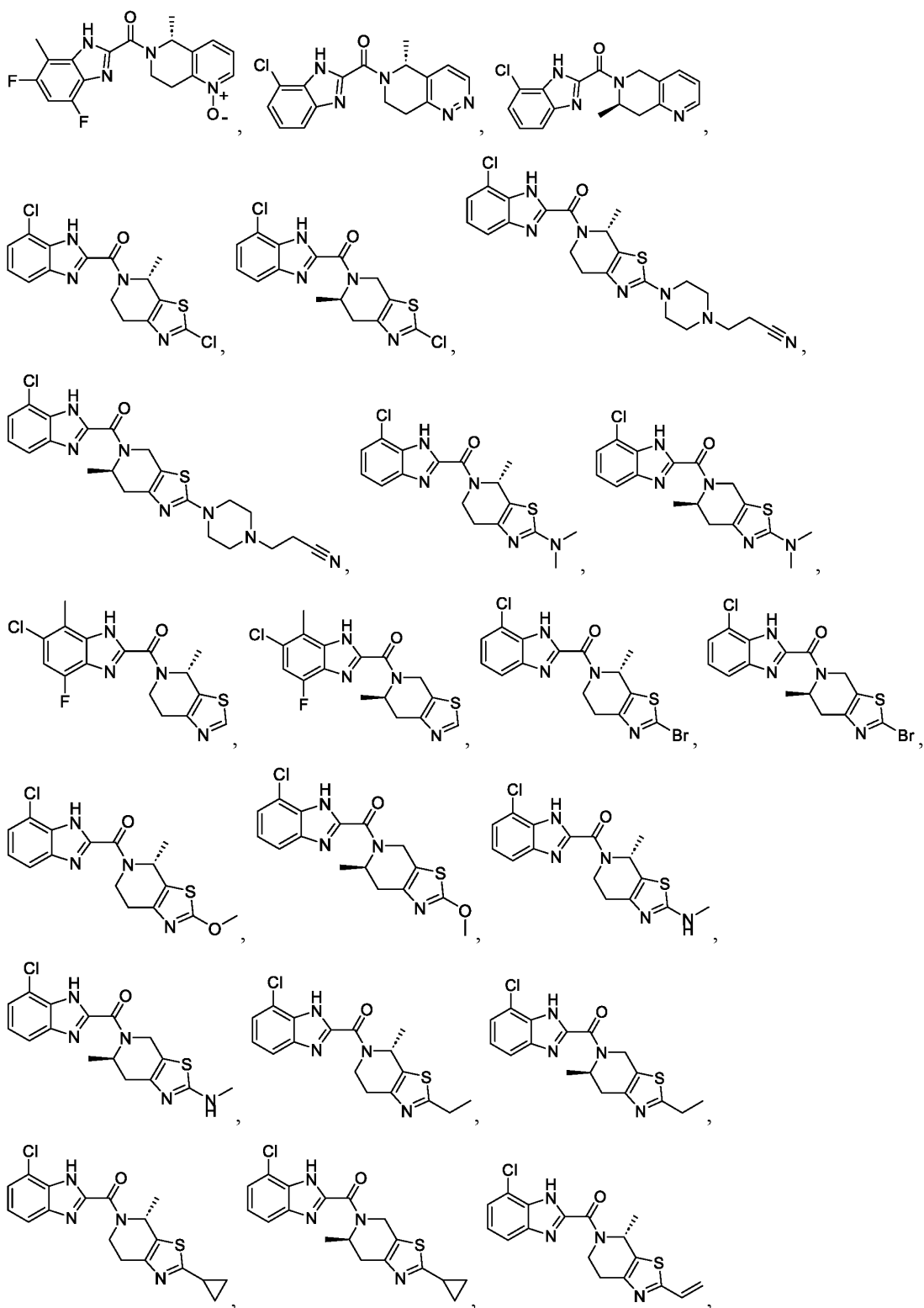


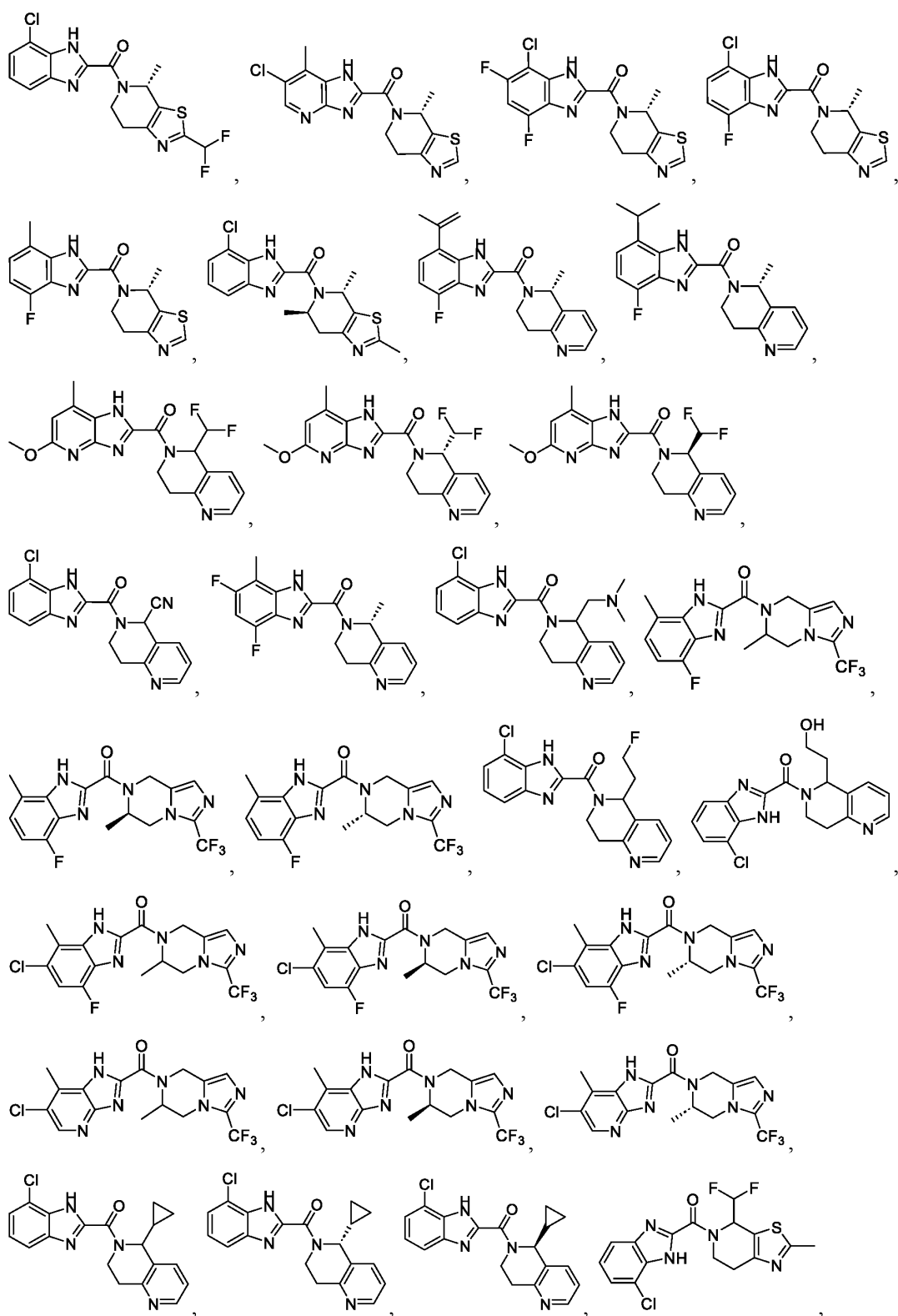


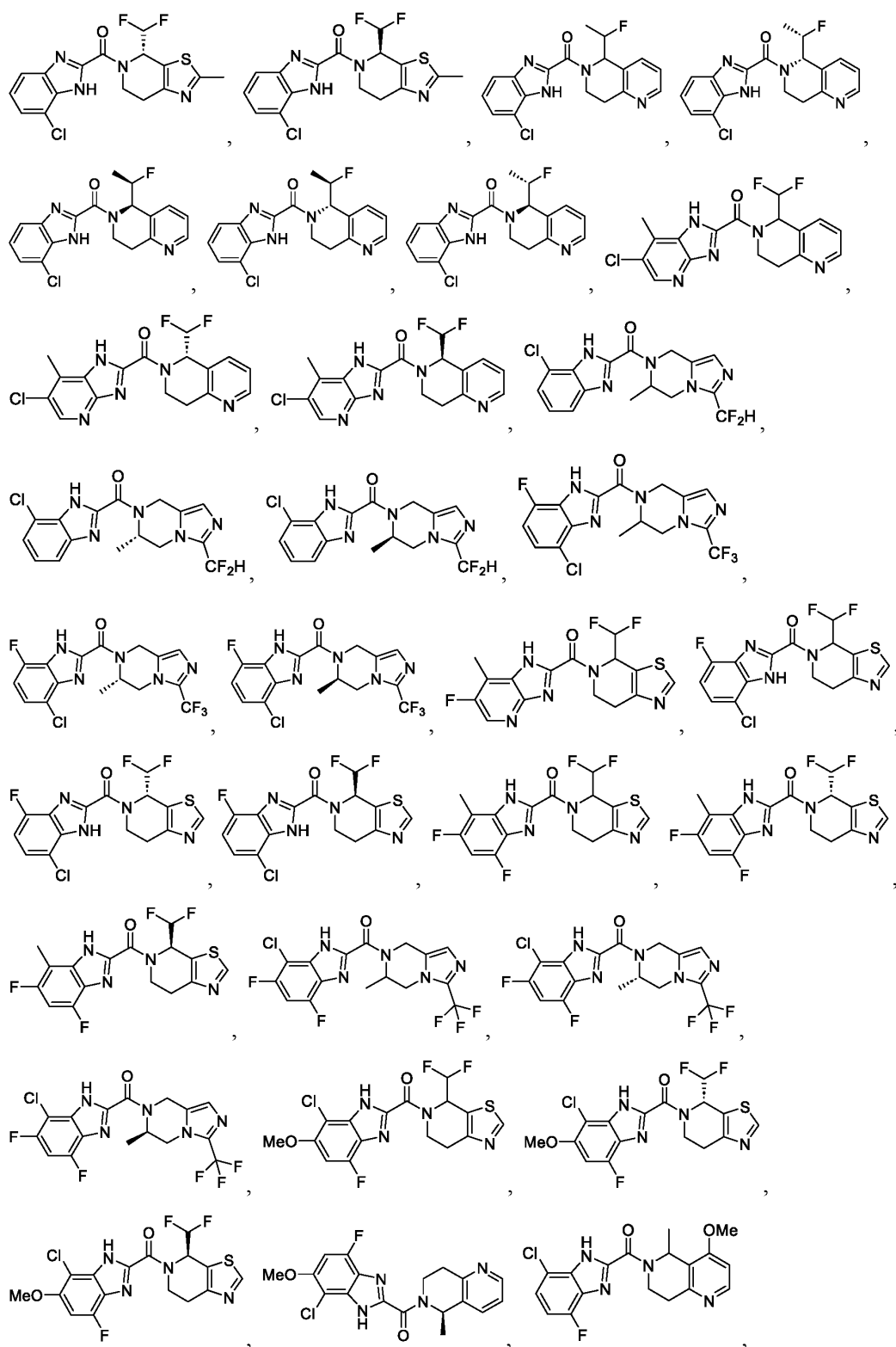


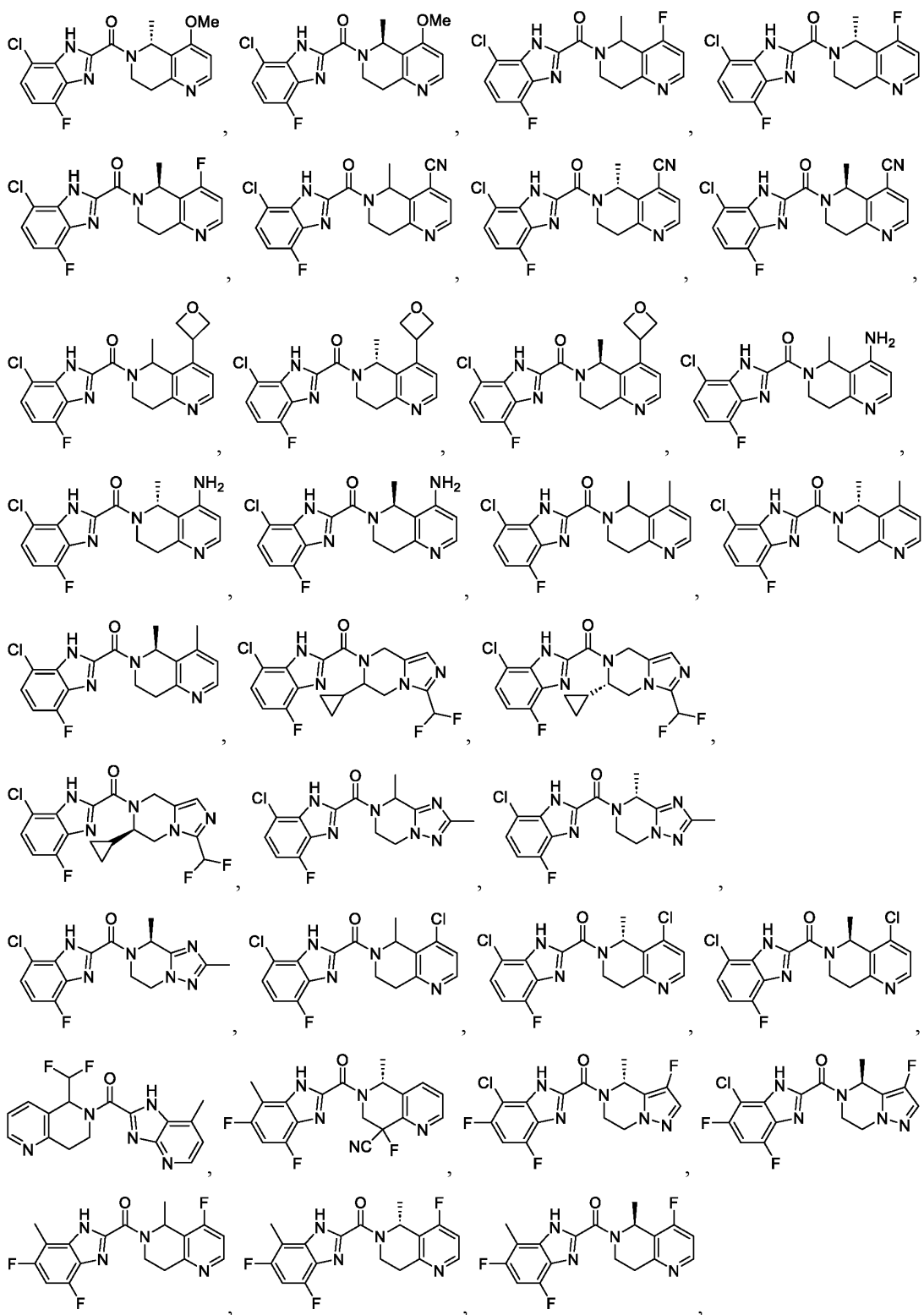
[00116] In some embodiments is a compound, or a pharmaceutically acceptable salt or solvate thereof, selected from:

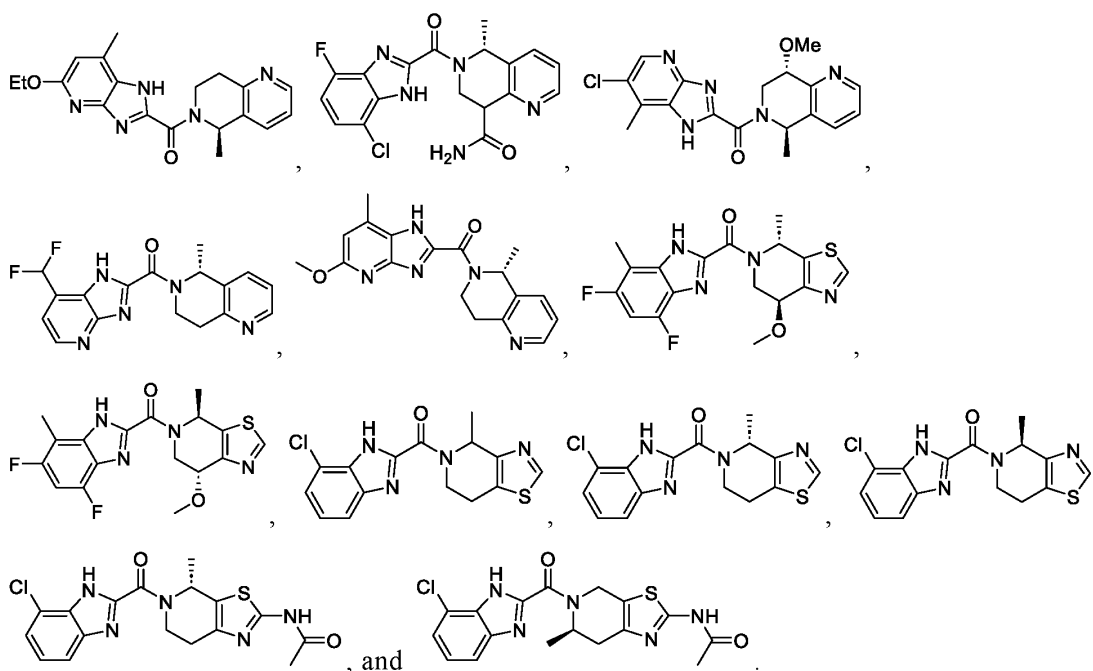












[00117] In some embodiments, compounds described herein are in the form of pharmaceutically acceptable salts. As well, active metabolites of these compounds having the same type of activity are included in the scope of the present disclosure. In addition, the compounds described herein can exist in unsolvated as well as solvated forms with pharmaceutically acceptable solvents such as water, ethanol, and the like. The solvated forms of the compounds presented herein are also considered to be disclosed herein.

[00118] “Pharmaceutically acceptable,” as used herein, refers a material, such as a carrier or diluent, which does not abrogate the biological activity or properties of the compound, and is relatively nontoxic, i.e., the material is administered to an individual without causing undesirable biological effects or interacting in a deleterious manner with any of the components of the composition in which it is contained.

[00119] The term “pharmaceutically acceptable salt” refers to a form of a therapeutically active agent that consists of a cationic form of the therapeutically active agent in combination with a suitable anion, or in alternative embodiments, an anionic form of the therapeutically active agent in combination with a suitable cation. Handbook of Pharmaceutical Salts: Properties, Selection and Use. International Union of Pure and Applied Chemistry, Wiley-VCH 2002. S.M. Berge, L.D. Bighley, D.C. Monkhouse, J. Pharm. Sci. 1977, 66, 1-19. P. H. Stahl and C. G. Wermuth, editors, *Handbook of Pharmaceutical Salts: Properties, Selection and Use*, Weinheim/Zürich: Wiley-VCH/VHCA, 2002. Pharmaceutical salts typically are more soluble and more rapidly soluble in stomach and intestinal juices than non-ionic species and so are useful in solid dosage

forms. Furthermore, because their solubility often is a function of pH, selective dissolution in one or another part of the digestive tract is possible, and this capability can be manipulated as one aspect of delayed and sustained release behaviors. Also, because the salt-forming molecule can be in equilibrium with a neutral form, passage through biological membranes can be adjusted.

[00120] In some embodiments, pharmaceutically acceptable salts are obtained by reacting a compound described herein with an acid to provide a "pharmaceutically acceptable acid addition salt." In some embodiments, the compound described herein (i.e. free base form) is basic and is reacted with an organic acid or an inorganic acid. Inorganic acids include, but are not limited to, hydrochloric acid, hydrobromic acid, sulfuric acid, phosphoric acid, nitric acid, and metaphosphoric acid. Organic acids include, but are not limited to, 1-hydroxy-2-naphthoic acid; 2,2-dichloroacetic acid; 2-hydroxyethanesulfonic acid; 2-oxoglutaric acid; 4-acetamidobenzoic acid; 4-aminosalicylic acid; acetic acid; adipic acid; ascorbic acid (L); aspartic acid (L); benzenesulfonic acid; benzoic acid; camphoric acid (+); camphor-10-sulfonic acid (+); capric acid (decanoic acid); caproic acid (hexanoic acid); caprylic acid (octanoic acid); carbonic acid; cinnamic acid; citric acid; cyclamic acid; dodecylsulfuric acid; ethane-1,2-disulfonic acid; ethanesulfonic acid; formic acid; fumaric acid; galactaric acid; gentisic acid; glucoheptonic acid (D); gluconic acid (D); glucuronic acid (D); glutamic acid; glutaric acid; glycerophosphoric acid; glycolic acid; hippuric acid; isobutyric acid; lactic acid (DL); lactobionic acid; lauric acid; maleic acid; malic acid (- L); malonic acid; mandelic acid (DL); methanesulfonic acid; monomethyl fumarate, naphthalene-1,5-disulfonic acid; naphthalene-2-sulfonic acid; nicotinic acid; oleic acid; oxalic acid; palmitic acid; pamoic acid; phosphoric acid; propionic acid; pyroglutamic acid (- L); salicylic acid; sebacic acid; stearic acid; succinic acid; sulfuric acid; tartaric acid (+ L); thiocyanic acid; toluenesulfonic acid (*p*); and undecylenic acid.

[00121] In some embodiments, a compound described herein is prepared as a chloride salt, sulfate salt, bromide salt, mesylate salt, maleate salt, citrate salt or phosphate salt.

[00122] In some embodiments, pharmaceutically acceptable salts are obtained by reacting a compound described herein with a base to provide a "pharmaceutically acceptable base addition salt."

[00123] In some embodiments, the compound described herein is acidic and is reacted with a base. In such situations, an acidic proton of the compound described herein is replaced by a metal ion, e.g., lithium, sodium, potassium, magnesium, calcium, or an aluminum ion. In some cases, compounds described herein coordinate with an organic base, such as, but not limited to, ethanolamine, diethanolamine, triethanolamine, tromethamine, meglumine, N-methylglucamine,

dicyclohexylamine, tris(hydroxymethyl)methylamine. In other cases, compounds described herein form salts with amino acids such as, but not limited to, arginine, lysine, and the like. Acceptable inorganic bases used to form salts with compounds that include an acidic proton, include, but are not limited to, aluminum hydroxide, calcium hydroxide, potassium hydroxide, sodium carbonate, potassium carbonate, sodium hydroxide, lithium hydroxide, and the like. In some embodiments, the compounds provided herein are prepared as a sodium salt, calcium salt, potassium salt, magnesium salt, meglumine salt, N-methylglucamine salt or ammonium salt.

[00124] It should be understood that a reference to a pharmaceutically acceptable salt includes the solvent addition forms. In some embodiments, solvates contain either stoichiometric or non-stoichiometric amounts of a solvent, and are formed during the process of isolating or purifying the compound with pharmaceutically acceptable solvents such as water, ethanol, and the like. Hydrates are formed when the solvent is water, or alcoholates are formed when the solvent is alcohol. Solvates of compounds described herein are conveniently prepared or formed during the processes described herein. In addition, the compounds provided herein optionally exist in unsolvated as well as solvated forms.

[00125] In some embodiments, sites on the organic radicals (e.g. alkyl groups, aromatic rings) of compounds described herein are susceptible to various metabolic reactions. Incorporation of appropriate substituents on the organic radicals will reduce, minimize or eliminate this metabolic pathway. In specific embodiments, the appropriate substituent to decrease or eliminate the susceptibility of the aromatic ring to metabolic reactions is, by way of example only, a halogen, deuterium, an alkyl group, a haloalkyl group, or a deuterioalkyl group.

[00126] In another embodiment, the compounds described herein are labeled isotopically (e.g. with a radioisotope) or by another other means, including, but not limited to, the use of chromophores or fluorescent moieties, bioluminescent labels, or chemiluminescent labels.

[00127] Compounds described herein include isotopically-labeled compounds, which are identical to those recited in the various formulae and structures presented herein, but for the fact that one or more atoms are replaced by an atom having an atomic mass or mass number different from the atomic mass or mass number usually found in nature. Examples of isotopes that can be incorporated into the present compounds include isotopes of hydrogen, carbon, nitrogen, oxygen, fluorine and chlorine, such as, for example, ^2H , ^3H , ^{13}C , ^{14}C , ^{15}N , ^{18}O , ^{17}O , ^{35}S , ^{18}F , ^{36}Cl . In one aspect, isotopically-labeled compounds described herein, for example those into which radioactive isotopes such as ^3H and ^{14}C are incorporated, are useful in drug and/or substrate tissue distribution assays. In one aspect, substitution with isotopes such as deuterium affords certain therapeutic advantages resulting from greater metabolic stability, such as, for example,

increased *in vivo* half-life or reduced dosage requirements. In some embodiments, one or more hydrogen atoms of the compounds described herein is replaced with deuterium.

[00128] In some embodiments, the compounds described herein possess one or more stereocenters and each stereocenter exists independently in either the R or S configuration. The compounds presented herein include all diastereomeric, enantiomeric, atropisomers, and epimeric forms as well as the appropriate mixtures thereof. The compounds and methods provided herein include all *cis*, *trans*, *syn*, *anti*, *entgegen* (E), and *zusammen* (Z) isomers as well as the appropriate mixtures thereof.

[00129] Individual stereoisomers are obtained, if desired, by methods such as, stereoselective synthesis and/or the separation of stereoisomers by chiral chromatographic columns. In certain embodiments, compounds described herein are prepared as their individual stereoisomers by reacting a racemic mixture of the compound with an optically active resolving agent to form a pair of diastereoisomeric compounds/salts, separating the diastereomers and recovering the optically pure enantiomers. In some embodiments, resolution of enantiomers is carried out using covalent diastereomeric derivatives of the compounds described herein. In another embodiment, diastereomers are separated by separation/resolution techniques based upon differences in solubility. In other embodiments, separation of stereoisomers is performed by chromatography or by the forming diastereomeric salts and separation by recrystallization, or chromatography, or any combination thereof. Jean Jacques, Andre Collet, Samuel H. Wilen, "Enantiomers, Racemates and Resolutions", John Wiley and Sons, Inc., 1981. In some embodiments, stereoisomers are obtained by stereoselective synthesis.

[00130] A tautomer refers to a molecule wherein a proton shift from one atom of a molecule to another atom of the same molecule is possible. In certain embodiments, the compounds presented herein exist as tautomers. In circumstances where tautomerization is possible, a chemical equilibrium of the tautomers will exist. The exact ratio of the tautomers depends on several factors, including physical state, temperature, solvent, and pH. The compounds presented herein include all tautomeric forms as well as the appropriate mixtures thereof.

Synthesis of Compounds

[00131] Compounds described herein are synthesized using standard synthetic techniques or using methods known in the art in combination with methods described herein.

[00132] Unless otherwise indicated, conventional methods of mass spectroscopy, NMR, HPLC, protein chemistry, biochemistry, recombinant DNA techniques and pharmacology are employed.

[00133] Compounds are prepared using standard organic chemistry techniques such as those described in, for example, March's Advanced Organic Chemistry, 6th Edition, John Wiley and

Sons, Inc. Alternative reaction conditions for the synthetic transformations described herein may be employed such as variation of solvent, reaction temperature, reaction time, as well as different chemical reagents and other reaction conditions. The starting materials are available from commercial sources or are readily prepared.

[00134] Suitable reference books and treatise that detail the synthesis of reactants useful in the preparation of compounds described herein, or provide references to articles that describe the preparation, include for example, "Synthetic Organic Chemistry", John Wiley & Sons, Inc., New York; S. R. Sandler et al., "Organic Functional Group Preparations," 2nd Ed., Academic Press, New York, 1983; H. O. House, "Modern Synthetic Reactions", 2nd Ed., W. A. Benjamin, Inc. Menlo Park, Calif. 1972; T. L. Gilchrist, "Heterocyclic Chemistry", 2nd Ed., John Wiley & Sons, New York, 1992; J. March, "Advanced Organic Chemistry: Reactions, Mechanisms and Structure", 4th Ed., Wiley-Interscience, New York, 1992. Additional suitable reference books and treatise that detail the synthesis of reactants useful in the preparation of compounds described herein, or provide references to articles that describe the preparation, include for example, Fuhrhop, J. and Penzlin G. "Organic Synthesis: Concepts, Methods, Starting Materials", Second, Revised and Enlarged Edition (1994) John Wiley & Sons ISBN: 3-527-29074-5; Hoffman, R. V. "Organic Chemistry, An Intermediate Text" (1996) Oxford University Press, ISBN 0-19-509618-5; Larock, R. C. "Comprehensive Organic Transformations: A Guide to Functional Group Preparations" 2nd Edition (1999) Wiley-VCH, ISBN: 0-471-19031-4; March, J. "Advanced Organic Chemistry: Reactions, Mechanisms, and Structure" 4th Edition (1992) John Wiley & Sons, ISBN: 0-471-60180-2; Otera, J. (editor) "Modern Carbonyl Chemistry" (2000) Wiley-VCH, ISBN: 3-527-29871-1; Patai, S. "Patai's 1992 Guide to the Chemistry of Functional Groups" (1992) Interscience ISBN: 0-471-93022-9; Solomons, T. W. G. "Organic Chemistry" 7th Edition (2000) John Wiley & Sons, ISBN: 0-471-19095-0; Stowell, J.C., "Intermediate Organic Chemistry" 2nd Edition (1993) Wiley-Interscience, ISBN: 0-471-57456-2; "Industrial Organic Chemicals: Starting Materials and Intermediates: An Ullmann's Encyclopedia" (1999) John Wiley & Sons, ISBN: 3-527-29645-X, in 8 volumes; "Organic Reactions" (1942-2000) John Wiley & Sons, in over 55 volumes; and "Chemistry of Functional Groups" John Wiley & Sons, in 73 volumes.

[00135] In some embodiments, compounds are prepared as described in the Examples.

Methods of Treatment

[00136] In some embodiments, described herein is a method of treating retinal degeneration in a subject in need thereof comprising administering to the patient a compound of Formula (I), (Ia), (II), (IIa), (II), (IIIa), (IV), or (IVa), or a pharmaceutically acceptable salt or solvate thereof. In

some embodiments is a method of treating autosomal dominant retinitis pigmentosa (adRP) in a subject in need thereof comprising administering to the patient a compound of Formula (I), (Ia), (II), (IIa), (II), (IIIa), (IV), or (IVa), or a pharmaceutically acceptable salt or solvate thereof.

Pharmaceutical compositions

[00137] In some embodiments, the compounds described herein are formulated into pharmaceutical compositions. Pharmaceutical compositions are formulated in a conventional manner using one or more pharmaceutically acceptable inactive ingredients that facilitate processing of the active compounds into preparations that are used pharmaceutically. Proper formulation is dependent upon the route of administration chosen. A summary of pharmaceutical compositions described herein is found, for example, in Remington: The Science and Practice of Pharmacy, Nineteenth Ed (Easton, Pa.: Mack Publishing Company, 1995); Hoover, John E., Remington's Pharmaceutical Sciences, Mack Publishing Co., Easton, Pennsylvania 1975; Liberman, H.A. and Lachman, L., Eds., Pharmaceutical Dosage Forms, Marcel Dekker, New York, N.Y., 1980; and Pharmaceutical Dosage Forms and Drug Delivery Systems, Seventh Ed. (Lippincott Williams & Wilkins 1999), herein incorporated by reference for such disclosure.

[00138] Administration of the compounds and compositions described herein can be affected by any method that enables delivery of the compounds to the site of action. These methods include, though are not limited to delivery via enteral routes (including oral, gastric or duodenal feeding tube, rectal suppository and rectal enema), parenteral routes (injection or infusion, including intraarterial, intracardiac, intradermal, intraduodenal, intramedullary, intramuscular, intraosseous, intraperitoneal, intrathecal, intravascular, intravenous, intravitreal, epidural and subcutaneous), inhalational, transdermal, transmucosal, sublingual, buccal and topical (including epicutaneous, dermal, enema, eye drops, ear drops, intranasal, vaginal) administration, although the most suitable route may depend upon for example the condition and disorder of the recipient.

[00139] In some embodiments, pharmaceutical compositions suitable for oral administration are presented 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 liquid or a non-aqueous liquid; or as an oil-in-water liquid emulsion or a water-in-oil liquid emulsion. In some embodiments, the active ingredient is presented as a bolus, electuary or paste.

[00140] Pharmaceutical compositions which can be used orally include tablets, push-fit capsules made of gelatin, as well as soft, sealed capsules made of gelatin and a plasticizer, such as glycerol or sorbitol. Tablets may be made by compression or molding, optionally with one or more accessory 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 binders, inert diluents, or lubricating, surface active or dispersing agents. Molded tablets may be made by molding in a suitable machine a mixture of the powdered compound moistened with an inert liquid diluent. In some embodiments, the tablets are coated or scored and are formulated so as to provide slow or controlled release of the active ingredient therein. All formulations for oral administration should be in dosages suitable for such administration. The push-fit capsules can contain the active ingredients in admixture with filler such as lactose, binders such as starches, and/or lubricants such as talc or magnesium stearate and, optionally, stabilizers. In soft capsules, the active compounds may be dissolved or suspended in suitable liquids, such as fatty oils, liquid paraffin, or liquid polyethylene glycols. In some embodiments, stabilizers are added. Dragee cores are provided with suitable coatings. For this purpose, concentrated sugar solutions may be used, which may optionally contain gum arabic, talc, polyvinyl pyrrolidone, carbopol gel, polyethylene glycol, and/or titanium dioxide, lacquer solutions, and suitable organic solvents or solvent mixtures. Dyestuffs or pigments may be added to the tablets or Dragee coatings for identification or to characterize different combinations of active compound doses.

[00141] In some embodiments, pharmaceutical compositions are formulated for parenteral administration by injection, e.g., by bolus injection or continuous infusion. Formulations for injection may be presented in unit dosage form, e.g., in ampoules or in multi-dose containers, with an added preservative. The compositions may take such forms as suspensions, solutions or emulsions in oily or aqueous vehicles, and may contain formulatory agents such as suspending, stabilizing and/or dispersing agents. The compositions may be presented in unit-dose or multi-dose containers, for example sealed ampoules and vials, and may be stored in powder form or in a freeze-dried (lyophilized) condition requiring only the addition of the sterile liquid carrier, for example, saline or sterile pyrogen-free water, immediately prior to use. Extemporaneous injection solutions and suspensions may be prepared from sterile powders, granules and tablets of the kind previously described.

[00142] Pharmaceutical compositions for parenteral administration include aqueous and non-aqueous (oily) sterile injection solutions of the active compounds which may contain antioxidants, 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. Suitable lipophilic solvents or vehicles include fatty oils such as sesame oil, or synthetic fatty acid esters, such as ethyl oleate or triglycerides, or liposomes. Aqueous injection suspensions may contain substances which increase the viscosity

of the suspension, such as sodium carboxymethyl cellulose, sorbitol, or dextran. Optionally, the suspension may also contain suitable stabilizers or agents which increase the solubility of the compounds to allow for the preparation of highly concentrated solutions.

[00143] Pharmaceutical compositions may also be formulated as a depot preparation. Such long acting formulations may be administered by implantation (for example subcutaneously or intramuscularly) or by intramuscular injection. Thus, for example, the compounds may be formulated with suitable polymeric or hydrophobic materials (for example, as an emulsion in an acceptable oil) or ion exchange resins, or as sparingly soluble derivatives, for example, as a sparingly soluble salt.

[00144] For buccal or sublingual administration, the compositions may take the form of tablets, lozenges, pastilles, or gels formulated in conventional manner. Such compositions may comprise the active ingredient in a flavored basis such as sucrose and acacia or tragacanth.

[00145] Pharmaceutical compositions may also be formulated in rectal compositions such as suppositories or retention enemas, e.g., containing conventional suppository bases such as cocoa butter, polyethylene glycol, or other glycerides.

[00146] Pharmaceutical compositions may be administered topically, that is by non-systemic administration. This includes the application of a compound of the present invention externally to the epidermis or the buccal cavity and the installation of such a compound into the ear, eye and nose, such that the compound does not significantly enter the blood stream. In contrast, systemic administration refers to oral, intravenous, intraperitoneal and intramuscular administration.

[00147] Pharmaceutical compositions suitable for topical administration include liquid or semi-liquid preparations suitable for penetration through the skin to the site of inflammation such as gels, liniments, lotions, creams, ointments or pastes, and drops suitable for administration to the eye, ear or nose. The active ingredient may comprise, for topical administration, from 0.001% to 10% w/w, for instance from 1% to 2% by weight of the formulation.

[00148] Pharmaceutical compositions for administration by inhalation are conveniently delivered from an insufflator, nebulizer pressurized packs or other convenient means of delivering an aerosol spray. Pressurized packs may comprise a suitable propellant such as dichlorodifluoromethane, trichlorofluoromethane, dichlorotetrafluoroethane, carbon dioxide or other suitable gas. In the case of a pressurized aerosol, the dosage unit may be determined by providing a valve to deliver a metered amount. Alternatively, for administration by inhalation or insufflation, pharmaceutical preparations may take the form of a dry powder composition, for example a powder mix of the compound and a suitable powder base such as lactose or starch.

The powder composition may be presented in unit dosage form, in for example, capsules, cartridges, gelatin or blister packs from which the powder may be administered with the aid of an inhalator or insufflator.

[00149] In some embodiments, a compound disclosed herein is formulated in such a manner that delivery of the compound to a particular region of the gastrointestinal tract is achieved. For example, a compound disclosed herein is formulated for oral delivery with bioadhesive polymers, pH-sensitive coatings, time dependent, biodegradable polymers, microflora activated systems, and the like, in order to effect delivering of the compound to a particular region of the gastrointestinal tract.

[00150] In some embodiments, a compound disclosed herein is formulated to provide a controlled release of the compound. Controlled release refers to the release of the compound described herein from a dosage form in which it is incorporated according to a desired profile over an extended period of time. Controlled release profiles include, for example, sustained release, prolonged release, pulsatile release, and delayed release profiles. In contrast to immediate release compositions, controlled release compositions allow delivery of an agent to a subject over an extended period of time according to a predetermined profile. Such release rates can provide therapeutically effective levels of agent for an extended period of time and thereby provide a longer period of pharmacologic response while minimizing side effects as compared to conventional rapid release dosage forms. Such longer periods of response provide for many inherent benefits that are not achieved with the corresponding short acting, immediate release preparations.

[00151] Approaches to deliver the intact therapeutic compound to the particular regions of the gastrointestinal tract (e.g. such as the colon), include:

[00152] (i) Coating with polymers: The intact molecule can be delivered to the colon without absorbing at the upper part of the intestine by coating of the drug molecule with the suitable polymers, which degrade only in the colon.

[00153] (ii) Coating with pH-sensitive polymers: The majority of enteric and colon targeted delivery systems are based on the coating of tablets or pellets, which are filled into conventional hard gelatin capsules. Most commonly used pH-dependent coating polymers are methacrylic acid copolymers, commonly known as Eudragit® S, more specifically Eudragit® L and Eudragit® S. Eudragit® L100 and S 100 are copolymers of methacrylic acid and methyl methacrylate.

[00154] (iii) Coating with biodegradable polymers;

[00155] (iv) Embedding in matrices;

[00156] (v) Embedding in biodegradable matrices and hydrogels;

[00157] (vi) Embedding in pH-sensitive matrices;

[00158] (vii) Timed release systems;

[00159] (viii) Redox-sensitive polymers;

[00160] (ix) Bioadhesive systems;

[00161] (x) Coating with microparticles;

[00162] (xi) Osmotic controlled drug delivery;

[00163] Another approach towards colon-targeted drug delivery or controlled-release systems includes embedding the drug in polymer matrices to trap it and release it in the colon. These matrices can be pH-sensitive or biodegradable. Matrix-Based Systems, such as multi-matrix (MMX)-based delayed-release tablets, ensure the drug release in the colon.

[00164] Additional pharmaceutical approaches to targeted delivery of therapeutics to particular regions of the gastrointestinal tract are known. Chourasia MK, Jain SK, Pharmaceutical approaches to colon targeted drug delivery systems., J Pharm Sci. 2003 Jan-Apr;6(1):33-66. Patel M, Shah T, Amin A. Therapeutic opportunities in colon-specific drug-delivery systems Crit Rev Ther Drug Carrier Syst. 2007;24(2):147-202. Kumar P, Mishra B. Colon targeted drug delivery systems--an overview. Curr Drug Deliv. 2008 Jul;5(3):186-98. Van den Mooter G. Colon drug delivery. Expert Opin Drug Deliv. 2006 Jan;3(1):111-25. Seth Amidon, Jack E. Brown, and Vivek S. Dave, Colon-Targeted Oral Drug Delivery Systems: Design Trends and Approaches, AAPS PharmSciTech. 2015 Aug; 16(4): 731–741.

[00165] It should be understood that in addition to the ingredients particularly mentioned above, the compounds and compositions described herein 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.

Methods of Dosing and Treatment Regimens

[00166] In one embodiment, the compounds described herein, or a pharmaceutically acceptable salt thereof, are used in the preparation of medicaments for the treatment of diseases or conditions in a mammal that would benefit from administration of a small molecule corrector of rhodopsin. Methods for treating any of the diseases or conditions described herein in a mammal in need of such treatment, involves administration of pharmaceutical compositions that include at least one compound described herein or a pharmaceutically acceptable salt, active metabolite, prodrug, or pharmaceutically acceptable solvate thereof, in therapeutically effective amounts to said mammal.

[00167] In certain embodiments, the compositions containing the compound(s) described herein are administered for prophylactic and/or therapeutic treatments. In certain therapeutic

applications, the compositions are administered to a patient already suffering from a disease or condition, in an amount sufficient to cure or at least partially arrest at least one of the symptoms of the disease or condition. Amounts effective for this use depend on the severity and course of the disease or condition, previous therapy, the patient's health status, weight, and response to the drugs, and the judgment of the treating physician. Therapeutically effective amounts are optionally determined by methods including, but not limited to, a dose escalation and/or dose ranging clinical trial.

[00168] In prophylactic applications, compositions containing the compounds described herein are administered to a patient susceptible to or otherwise at risk of a particular disease, disorder or condition. Such an amount is defined to be a "prophylactically effective amount or dose." In this use, the precise amounts also depend on the patient's state of health, weight, and the like. When used in patients, effective amounts for this use will depend on the severity and course of the disease, disorder or condition, previous therapy, the patient's health status and response to the drugs, and the judgment of the treating physician. In one aspect, prophylactic treatments include administering to a mammal, who previously experienced at least one symptom of the disease being treated and is currently in remission, a pharmaceutical composition comprising a compound described herein, or a pharmaceutically acceptable salt thereof, in order to prevent a return of the symptoms of the disease or condition.

[00169] In certain embodiments, wherein the patient's condition does not improve, upon the doctor's discretion, the compounds are administered chronically, that is, for an extended period of time, including throughout the duration of the patient's life in order to ameliorate or otherwise control or limit the symptoms of the patient's disease or condition.

[00170] In certain embodiments, wherein a patient's status does improve, the dose of drug being administered is temporarily reduced or temporarily suspended for a certain length of time (*i.e.*, a "drug holiday"). In specific embodiments, the length of the drug holiday is between 2 days and 1 year, including by way of example only, 2 days, 3 days, 4 days, 5 days, 6 days, 7 days, 10 days, 12 days, 15 days, 20 days, 28 days, or more than 28 days. The dose reduction during a drug holiday is, by way of example only, by 10%-100%, including by way of example only 10%, 15%, 20%, 25%, 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, and 100%.

[00171] Once improvement of the patient's conditions has occurred, a maintenance dose is administered if necessary. Subsequently, in specific embodiments, the dosage or the frequency of administration, or both, is reduced, as a function of the symptoms, to a level at which the

improved disease, disorder or condition is retained. In certain embodiments, however, the patient requires intermittent treatment on a long-term basis upon any recurrence of symptoms.

[00172] The amount of a given agent that corresponds to such an amount varies depending upon factors such as the particular compound, disease condition and its severity, the identity (*e.g.*, weight, sex) of the subject or host in need of treatment, but nevertheless is determined according to the particular circumstances surrounding the case, including, *e.g.*, the specific agent being administered, the route of administration, the condition being treated, and the subject or host being treated.

[00173] In general, however, doses employed for adult human treatment are typically in the range of 0.01 mg-5000 mg per day. In one aspect, doses employed for adult human treatment are from about 1 mg to about 1000 mg per day. In one embodiment, the desired dose is conveniently presented in a single dose or in divided doses administered simultaneously or at appropriate intervals, for example as two, three, four or more sub-doses per day.

[00174] Toxicity and therapeutic efficacy of such therapeutic regimens are determined by standard pharmaceutical procedures in cell cultures or experimental animals, including, but not limited to, the determination of the LD₅₀ and the ED₅₀. The dose ratio between the toxic and therapeutic effects is the therapeutic index and it is expressed as the ratio between LD₅₀ and ED₅₀. In certain embodiments, the data obtained from cell culture assays and animal studies are used in formulating the therapeutically effective daily dosage range and/or the therapeutically effective unit dosage amount for use in mammals, including humans. In some embodiments, the daily dosage amount of the compounds described herein lies within a range of circulating concentrations that include the ED₅₀ with minimal toxicity. In certain embodiments, the daily dosage range and/or the unit dosage amount varies within this range depending upon the dosage form employed and the route of administration utilized.

[00175] In any of the aforementioned aspects are further embodiments in which the effective amount of the compound described herein, or a pharmaceutically acceptable salt thereof, is: (a) systemically administered to the mammal; and/or (b) administered orally to the mammal; and/or (c) intravenously administered to the mammal; and/or (d) administered by injection to the mammal; and/or (e) administered topically to the mammal; and/or (f) administered non-systemically or locally to the mammal.

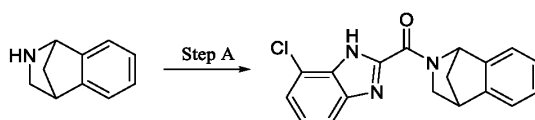
EXAMPLES

[00176] The following examples are provided for illustrative purposes only and not to limit the scope of the claims provided herein.

[00177] As used above, and throughout the description of the invention, the following abbreviations, unless otherwise indicated, shall be understood to have the following meanings:

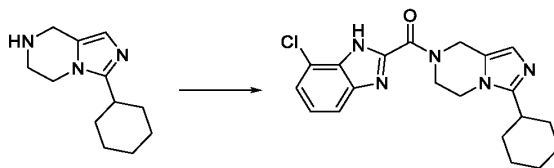
Example 1: (7-Chloro-1H-benzo[d]imidazol-2-yl)(3,4-dihydro-1,4-methanoisoquinolin-2(1H)-yl)methanone

ACN, MeCN	Acetonitrile
AcOH	Acetic acid
AmB	Ammonium bicarbonate
AmF	Ammonium formate
aq.	aqueous
anh.	anhydrous
Boc	<i>tert</i> -butoxy carbonyl
CV	Column Volume
DCE	1,2-dichloroethane
DCM	Dichloromethane
DMAc	Dimethylacetamide
DIPEA, iPrNEt ₂	<i>N,N</i> -Diisopropyl ethylamine
DME	1,2-Dimethoxyethane
DMF	Dimethylformamide
DMSO	Dimethylsulfoxide
eq(s).	equivalent(s)
EtOAc	Ethyl acetate
Et ₃ N	Triethylamine
FA	Formic Acid
g	gram(s)
h	hour(s)
K ₂ CO ₃	Potassium carbonate
LCMS	liquid chromatography mass spectrometry
MeOH	Methanol
mg	milligram(s)
min	Minute(s)
mL	milliliter(s)
NaOH	Sodium hydroxide
Na ₂ SO ₄	Sodium sulfate
NMP	<i>N</i> -Methyl-2-pyrrolidone
NMR	Nuclear magnetic resonance
Ph	phenyl
PPA	Polyphosphoric acid
PTSA	<i>p</i> -Toluenesulfonic acid
r. t.	Room temperature
RT	Retention time
TFA	Trifluoroacetic acid
THF	Tetrahydrofuran
THP	3,4-Dihydro-2H-pyran
Ts	Toluenesulfonyl
UPLC-MS	Ultra-performance liquid chromatography-mass spectrometry



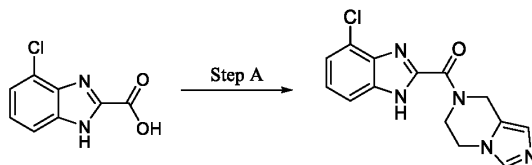
[00178] Step A: To a solution of 1,2,3,4-tetrahydro-1,4-methanoisoquinoline (50.0 mg, 0.275 mmol) in DMF (1.00 mL) was added 7-chloro-1H-benzo[d]imidazole-2-carboxylic acid (54.1 mg, 0.275 mmol), DIEA (71.1 mg, 0.550 mmol) and HATU (52.3 mg, 0.138 mmol). The mixture was stirred at 25 °C for 1 h. The reaction mixture was poured into H₂O (2.00 mL) and extracted with EtOAc (1.00 mL x 3). The combined organic layers were washed with brine (1.00 mL x 3), dried over Na₂SO₄, filtered, and concentrated under vacuum to give a residue which was purified by prep-HPLC (Phenomenex Luna C18 column (100 × 40 mm, 5 μm); flow rate: 25 mL/min; gradient: 35% – 65% B over 8 min; mobile phase A: 0.04% aqueous HCl, mobile phase B: acetonitrile) to afford (7-chloro-1H-benzo[d]imidazol-2-yl)(3,4-dihydro-1,4-methanoisoquinolin-2(1H)-yl)methanone. LC-MS: 324.1 [M+H]⁺. ¹H NMR (400 MHz, CDCl₃) δ 10.96 – 10.06 (m, 1H), 7.47 – 7.29 (m, 4H), 7.24 – 7.07 (m, 3H), 5.80 – 3.00 (m, 4H), 2.21 – 2.05 (m, 2H).

Example 2: (7-Chloro-1H-benzo[d]imidazol-2-yl)(3-cyclohexyl-5,6-dihydroimidazo[1,5-a]pyrazin-7(8H)-yl)methanone



[00179] The title compound was prepared from 3-cyclohexyl-5,6,7,8-tetrahydroimidazo[1,5-a]pyrazine and 7-chloro-1H-benzo[d]imidazole-2-carboxylic acid according to the procedure of Example 1, Step A. LC-MS: 384.2 [M+H]⁺. ¹H NMR (400 MHz, CDCl₃) δ 15.02 – 14.16 (m, 1H), 7.87 – 7.62 (m, 1H), 7.50 – 7.31 (m, 2H), 5.83 – 3.97 (m, 6H), 3.02 – 2.74 (m, 1H), 2.03 – 1.31 (m, 11H).

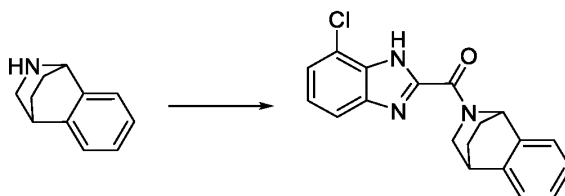
Example 3: (4-Chloro-1H-benzimidazol-2-yl)-(6,8-dihydro-5H-imidazo[1,5-a]pyrazin-7-yl)methanone



[00180] Step A: To a solution of 4-chloro-1H-benzimidazole-2-carboxylic acid (70.0 mg, 0.356 mmol) in DCM (2.00 mL) was added BOP-Cl (136 mg, 0.534 mmol) and TEA (149 μL, 1.10

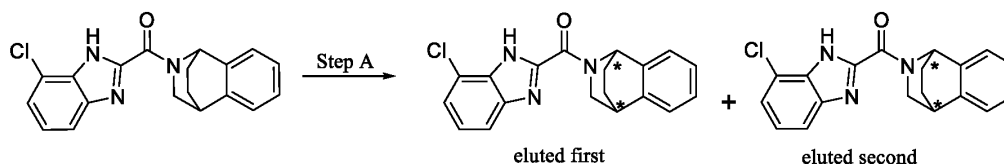
mmol) at 0 °C. The reaction mixture was stirred at 20 °C for 1 h. Then 5,6,7,8-tetrahydroimidazo[1,5-*a*]pyrazine (43.8 mg, 0.356 mmol) was added to the above solution and stirred at 20 °C for 12 h. The reaction mixture was concentrated under vacuum to give a residue. The residue was dissolved in DMF (2.0 mL), and purified by preparative-HPLC (Phenomenex Luna C18 column 100×40mm×5μm); flow rate: 25 mL/min; gradient: 1% – 30% B over 8 min; mobile phase A: 0.04% aqueous HCl, mobile phase B: acetonitrile) to afford (4-chloro-1*H*-benzimidazol-2-yl)-(6,8-dihydro-5*H*-imidazo[1,5-*a*]pyrazin-7-yl)methanone. LC-MS: 302.1 [M+H]⁺. ¹H NMR (400 MHz, DMSO-*d*₆) δ 9.19 (br d, *J* = 4.50 Hz, 1 H), 7.52 – 7.69 (m, 2 H), 7.24 – 7.47 (m, 2 H), 5.79 (s, 1 H), 5.03 (s, 1 H), 4.89 (br t, *J* = 4.63 Hz, 1 H), 4.36 – 4.58 (m, 2 H), 4.18 (br d, *J* = 4.63 Hz, 1 H).

Example 4: rac-(7-Chloro-1*H*-benzo[d]imidazol-2-yl)((1*S*,4*R*)-1,2,3,4-tetrahydro-1,4-(epiminomethano)naphthalen-10-yl)methanone



[00181] The title compound was prepared from rac-(1*S*,4*R*)-1,2,3,4-tetrahydro-1,4-(epiminomethano)naphthalene and 7-chloro-1*H*-benzo[d]imidazole-2-carboxylic acid according to the procedure of Example 1, Step A. LC-MS: 338.1 [M+H]⁺. ¹H NMR (400 MHz, DMSO-*d*₆) δ 13.61 – 13.21 (m, 1H), 7.57 – 7.20 (m, 7H), 7.05 – 5.69 (m, 1H), 4.37 – 3.46 (m, 2H), 3.27 – 3.18 (m, 1H), 2.34 – 1.98 (m, 2H), 1.65 – 1.40 (m, 2H).

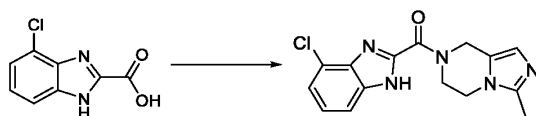
Examples 4A and 4B: (4-Chloro-1*H*-benzo[d]imidazol-2-yl)((1*S*,4*R*)-1,2,3,4-tetrahydro-1,4-(epiminomethano)naphthalen-10-yl)methanone and (4-Chloro-1*H*-benzo[d]imidazol-2-yl)((1*R*,4*S*)-1,2,3,4-tetrahydro-1,4-(epiminomethano)naphthalen-10-yl)methanone



[00182] **Step A:** rac-(7-Chloro-1*H*-benzo[d]imidazol-2-yl)((1*S*,4*R*)-1,2,3,4-tetrahydro-1,4-(epiminomethano)naphthalen-10-yl)methanone (**Example 4**) (39.5 mg, 0.117 mmol) was separated by SFC separation (Phenomenex-DAICEL CHIRALPAK AD (250 × 30 mm, 10 μm); flow rate: 30 mL/min; gradient: 50% B over 14 min; mobile phase A: heptane, mobile phase B: EtOH(0.1% NH₃H₂O) to afford a first eluted compound and a second eluted compound. First

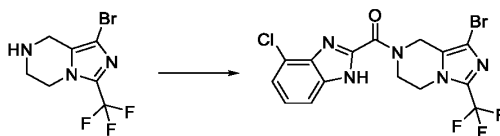
eluted compound (**Example 4A**): LC-MS: 338.1 $[M+H]^+$. 1H NMR (400 MHz, $CDCl_3$) δ 10.54 – 10.13 (m, 1H), 8.03 – 7.29 (m, 7H), 7.25 – 5.89 (m, 1H), 4.66 – 3.26 (m, 3H), 2.43 – 2.01 (m, 2H), 1.81 – 1.65 (m, 2H). Second eluted compound (**Example 4B**): LC-MS: 338.1 $[M+H]^+$. 1H NMR (400 MHz, $CDCl_3$) δ 10.60 – 10.17 (m, 1H), 7.96 – 7.28 (m, 8H), 4.62 – 3.41 (m, 3H), 2.40 – 1.99 (m, 2H), 1.81 – 1.65 (m, 2H). The absolute stereochemistry for the first and second eluted compounds was not determined.

Example 5: (4-Chloro-1H-benzimidazol-2-yl)-(3-methyl-6,8-dihydro-5H-imidazo[1,5-a]pyrazin-7-yl)methanone



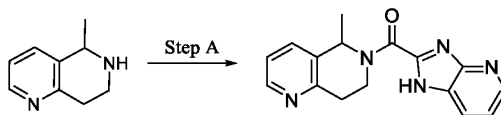
[00183] The title compound was prepared from 3-methyl-5,6,7,8-tetrahydroimidazo[1,5-a]pyrazine and 4-chloro-1H-benzimidazole-2-carboxylic acid according to the procedure of Example 3, Step A. LC-MS: 316.2 $[M+H]^+$. 1H NMR (400 MHz, $DMSO-d_6$) δ 7.46 – 7.60 (m, 2 H), 7.27 – 7.44 (m, 2 H), 5.78 (s, 1 H), 5.00 (s, 1 H), 4.92 (br t, $J=4.82$ Hz, 1 H), 4.37 (br t, $J=5.25$ Hz, 1 H), 4.10 – 4.30 (m, 2 H), 2.54 – 2.62 (m, 3 H).

Example 6: (1-Bromo-3-(trifluoromethyl)-5,6-dihydroimidazo[1,5-a]pyrazin-7(8H)-yl)(4-chloro-1H-benzo[d]imidazol-2-yl)methanone



[00184] The title compound was prepared from 1-bromo-3-(trifluoromethyl)-5,6,7,8-tetrahydroimidazo[1,5-a]pyrazine and 4-chloro-1H-benzo[d]imidazole-2-carboxylic acid according to the procedure of Example 1, Step A. LC-MS: 450.0 $[M+H]^+$. 1H NMR (400 MHz, $CDCl_3$) δ 10.64 – 10.20 (m, 1H), 7.90 – 7.45 (m, 1H), 7.44 – 7.38 (m, 1H), 7.37 – 7.28 (m, 1H), 6.13 – 4.26 (m, 6H).

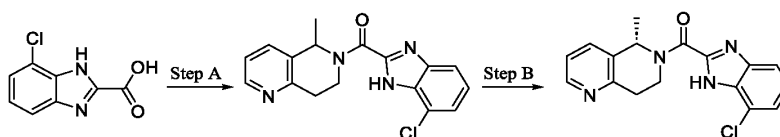
Example 7: (1H-Imidazo[4,5-b]pyridin-2-yl)(5-methyl-7,8-dihydro-1,6-naphthyridin-6(5H)-yl)methanone



[00185] **Step A:** To a solution of 1H-imidazo[4,5-b]pyridine-2-carboxylic acid (10.0 mg, 0.061 mmol) and 5-methyl-5,6,7,8-tetrahydro-1,6-naphthyridine (9.08 mg, 0.057 mmol) in DMF (1.00 mL) was added EDCI (14.1 mg, 0.735 mmol), TEA (18.6 mg, 0.184 mmol) and HOBt (9.94 mg,

0.073 mmol). The mixture was stirred at 20 °C for 1 h. The reaction mixture was poured into H₂O (5.00 mL) and washed with EtOAc (3.00 mL x 3). The combined organic layers were dried over Na₂SO₄, filtered, and concentrated under vacuum to give a residue which was purified by preparative HPLC (Phenomenex Gemini C18 column (80×30 mm, 3 μm); flow rate: 25 mL/min; gradient: 1% – 20% B over 8 min; mobile phase A: HCl: 0.04%, mobile phase B: acetonitrile) to afford (1H-imidazo[4,5-b]pyridin-2-yl)(5-methyl-7,8-dihydro-1,6-naphthyridin-6(5H)-yl)methanone. LC-MS: 294.1 [M+H]⁺.

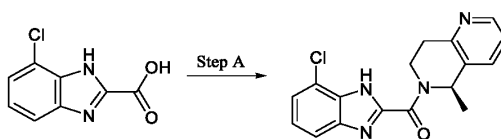
Example 8: (S)-(7-Chloro-1H-benzo[d]imidazol-2-yl)(5-methyl-7,8-dihydro-1,6-naphthyridin-6(5H)-yl)methanone



[00186] Step A: A mixture of 5-methyl-5,6,7,8-tetrahydro-1,6-naphthyridine (1.40 g, 9.45 mmol), 7-chloro-1H-benzimidazole-2-carboxylic acid (2.22 g, 4.34 mmol), HATU (1.80 g, 4.7 mmol) and DIEA (3.60 g, 28.0 mmol) in DMF (35.0 mL) was stirred at 20 °C for 1 h. The reaction mixture was poured into H₂O (30.0 mL) and extracted with EtOAc (30.0 mL x 3). The combined organic layers were dried over Na₂SO₄, filtered, and concentrated under vacuum to give a residue which was purified by preparative HPLC (column: Waters Xbridge C18 (150 × 50 mm, 10 μm); flow rate: [H₂O (10mM NH₄HCO₃)-ACN]; gradient: 20% – 50% B over 8 min; mobile phase A: 10mM aqueous NH₄HCO₃, mobile phase B: acetonitrile) to afford (7-chloro-1H-benzimidazol-2-yl)-(5-methyl-7,8-dihydro-5H-1,6-naphthyridin-6-yl)methanone. LC-MS: 327.1 [M+H]⁺. ¹H NMR (400 MHz, CDCl₃) δ 8.49 – 8.30 (m, 1H), 7.85 – 7.74 (m, 1H), 7.86 – 7.47 (m, 1H), 7.40 – 7.28 (m, 3H), 5.82 (br d, *J* = 6.4 Hz, 1H), 3.90 – 3.34 (m, 2H), 3.22 – 2.78 (m, 2H), 1.79 – 1.65 (m, 3H).

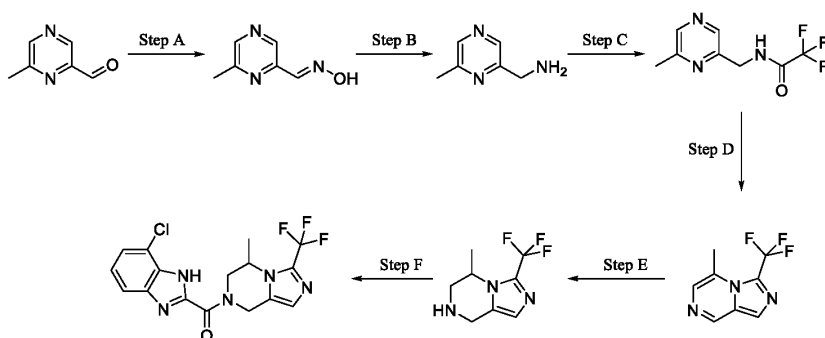
[00187] Step B: (7-Chloro-1H-benzimidazol-2-yl)-(5-methyl-7,8-dihydro-5H-1,6-naphthyridin-6-yl)methanone (1.4 g, 4.0 mmol) was further separated by SFC separation ((s,s) ChiralPak IH (250 × 30 mm, 10 μm); flow rate: 70 mL/min; gradient: 15-30% B over 12 min; mobile phase A: heptane, mobile phase B: EtOH(0.1% NH₃H₂O)) to afford (S)-(7-chloro-1H-benzo[d]imidazol-2-yl)(5-methyl-7,8-dihydro-1,6-naphthyridin-6(5H)-yl)methanone (second eluent). LC-MS: 327.1 [M+H]⁺. ¹H NMR (400 MHz, CD₃OD) δ 8.45 – 8.30 (m, 1H), 7.83 – 7.47 (m, 2H), 7.41 – 7.19 (m, 3H), 5.87 – 5.45 (m, 1H), 4.89 (br s, 1H), 3.84 – 3.65 (m, 1H), 3.84 – 3.33 (m, 1H), 3.17 – 2.98 (m, 1H), 1.80 – 1.60 (m, 3H).

Example 9: (R)-(7-Chloro-1H-benzo[d]imidazol-2-yl)(5-methyl-7,8-dihydro-1,6-naphthyridin-6(5H)-yl)methanone



[00188] Step A: A mixture of (R)-5-methyl-5,6,7,8-tetrahydro-1,6-naphthyridine (890 mg, 4.65 mmol), 7-chloro-1H-benzimidazole-2-carboxylic acid (1.10 g, 5.58 mmol), HATU (885 mg, 2.30 mmol) and DIEA (1.80 g, 14.0 mmol) in DMF (15.0 mL) was stirred at 20 °C for 1 h. The reaction mixture was poured into H₂O (20.0 mL) and extracted with EtOAc (20.0 mL x 3). The combined organic layers were dried over Na₂SO₄, filtered, and concentrated under vacuum to give a residue which was purified by preparative HPLC (column: Waters Xbridge C18 (150 × 50 mm, 10 μm); flow rate: [H₂O (10mM NH₄HCO₃)-ACN]; gradient: 20% – 50% B over 8 min; mobile phase A: 10mM aqueous NH₄HCO₃, mobile phase B: acetonitrile) to afford (R)-(7-chloro-1H-benzo[d]imidazol-2-yl)(5-methyl-7,8-dihydro-1,6-naphthyridin-6(5H)-yl)methanone. LC-MS: 327.1 [M+H]⁺. ¹H NMR (400 MHz, CD₃OD) δ 8.48 – 8.30 (m, 1H), 7.84 – 7.50 (m, 2H), 7.41 – 7.16 (m, 3H), 5.81 (br d, *J* = 6.8 Hz, 1H), 4.89 (br s, 1H), 3.81 – 3.32 (m, 2H), 3.17 – 2.99 (m, 1H), 1.80 – 1.63 (m, 3H).

Example 10: (7-Chloro-1H-benzo[d]imidazol-2-yl)(5-methyl-3-(trifluoromethyl)-5,6-dihydroimidazo[1,5-a]pyrazin-7(8H)-yl)methanone



[00189] Step A: To a solution of 6-methylpyrazine-2-carbaldehyde (1.80 g, 14.7 mmol) in EtOH (45.0 mL) was added NH₂OH.HCl (1.23 g, 17.7 mmol) and NaOAc (1.63 g, 19.9 mmol) in H₂O (25.0 mL). The mixture was stirred at 80 °C for 2 h. The mixture was concentrated under vacuum to give (E)-6-methylpyrazine-2-carbaldehyde oxime. LC-MS: 138.3 [M+H]⁺.

[00190] Step B: To a solution of (E)-6-methylpyrazine-2-carbaldehyde oxime (1.70 g, 12.4 mmol) in MeOH (50.0 mL) was added palladium on carbon (2.00 g, 10% purity) under a nitrogen atmosphere. The suspension was degassed and purged with hydrogen and repeated three times. The mixture was stirred at 20 °C for 12 h under a hydrogen (15 Psi) atmosphere. The suspension was filtered through a pad of Celite and the pad was washed with MeOH (10.0 mL ×

3). The combined filtrates were concentrated under vacuum to give a residue which was purified by flash silica gel chromatography using a gradient of EtOAc/petroleum ether from 1/100 to 1/3 to afford 6-methylpyrazin-2-yl)methanamine. LC-MS: 124.3 [M+H]⁺.

[00191] Step C: To a solution of (6-methylpyrazin-2-yl)methanamine (410 mg, 3.33 mmol) in DCM (10.0 mL) was added TFAA (0.50 mL, 3.99 mmol) at -10 °C. The mixture was stirred at 20 °C for 2 h. The mixture was concentrated under vacuum to give a residue which was purified by flash silica gel chromatography using a gradient of EtOAc/petroleum ether from 1/100 to 1/3 to afford 2,2,2-trifluoro-N-((6-methylpyrazin-2-yl)methyl)acetamide. LC-MS: 220.2 [M+H]⁺.

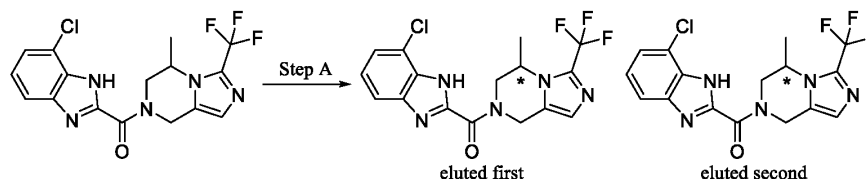
[00192] Step D: A solution of 2,2,2-trifluoro-N-((6-methylpyrazin-2-yl)methyl)acetamide (370 mg, 1.69 mmol) in POCl₃ (6.91 g, 451 mmol) was stirred at 130 °C for 5 h. The mixture was concentrated under vacuum to give a residue and then poured into ice-water (5.00 mL), treated with saturated Na₂CO₃ aqueous (5.00 mL) to pH = 8, and extracted with EtOAc (5.00 mL x 2). The combined organic phase was washed with H₂O (2.00 mL x 2) and brine (2.00 mL), dried over Na₂SO₄, filtered and concentrated to give a residue which was purified by flash silica gel chromatography using a gradient of EtOAc/petroleum ether from 0/1 to 1/0 to afford 5-methyl-3-(trifluoromethyl)imidazo[1,5-a]pyrazine. LC-MS: 202.2 [M+H]⁺.

[00193] Step E: To a solution of 5-methyl-3-(trifluoromethyl)imidazo[1,5-a]pyrazine (35.0 mg, 0.174 mmol) in 2,2,2-trifluoroethanol (1.00 mL) was added palladium on carbon (185 mg, 10% purity) under a nitrogen atmosphere. The suspension was degassed and purged with hydrogen and repeated three times. The mixture was stirred at 20 °C for 6 h under a hydrogen (15 Psi.) atmosphere. The suspension was filtered through a pad of Celite and the cake was washed with 2,2,2-trifluoroethanol (2.00 mL x 3). The combined filtrates were concentrated under vacuum to give 5-methyl-3-(trifluoromethyl)-5,6,7,8-tetrahydroimidazo[1,5-a]pyrazine. LC-MS: 206.2 [M+H]⁺.

[00194] Step F: To a solution of 5-methyl-3-(trifluoromethyl)imidazo[1,5-a]pyrazine (30.0 mg, 0.146 mmol), 7-chloro-1H-benzo[d]imidazole-2-carboxylic acid (28.7 mg, 0.146 mmol), HATU (16.7 mg, 0.044 mmol) in DMF (1.00 mL) was added DIEA (0.051 mL, 0.292 mmol). The mixture was stirred at 25 °C for 1 h. The mixture was poured into H₂O (1.00 mL) and extracted with DCM (1.00 mL x 3). The combined organic layers were dried over Na₂SO₄, filtered, and concentrated under vacuum to give a residue which was purified by preparative HPLC (Phenomenex Luna C18 column (75 × 30 mm, 3 μm); flow rate: 25 mL/min; gradient: 35% – 65% B over 8 min; mobile phase A: 0.04% aqueous HCl mobile phase B: acetonitrile). The relevant fractions were lyophilized to afford (7-chloro-1H-benzo[d]imidazol-2-yl)(5-methyl-3-(trifluoromethyl)-5,6-dihydroimidazo[1,5-a]pyrazin-7(8H)-yl)methanone. LC-MS: 384.1

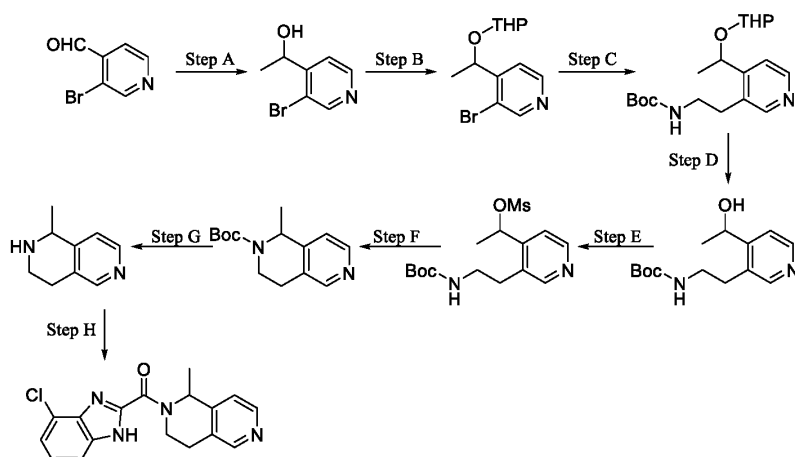
$[M+H]^+$. ^1H NMR (400 MHz, CD_3OD) δ 7.65 – 7.56 (m, 1H), 7.43 – 7.30 (m, 2H), 7.17 – 7.07 (m, 1H), 6.20 (br d, $J = 13.8$ Hz, 1H), 5.10 (br d, $J = 17.3$ Hz, 1H), 5.01 – 4.93 (m, 1H), 4.70 – 4.60 (m, 1H), 3.96 – 3.58 (m, 1H), 1.66 – 1.51 (m, 3H).

Examples 10A and 10B: (R) or (S)-(7-Chloro-1H-benzo[d]imidazol-2-yl)(5-methyl-3-(trifluoromethyl)-5,6-dihydroimidazo[1,5-a]pyrazin-7(8H)-yl)methanone and (R) or (S)-(7-Chloro-1H-benzo[d]imidazol-2-yl)(5-methyl-3-(trifluoromethyl)-5,6-dihydroimidazo[1,5-a]pyrazin-7(8H)-yl)methanone



[00195] Step A: (7-Chloro-1H-benzo[d]imidazol-2-yl)(5-methyl-3-(trifluoromethyl)-5,6-dihydroimidazo[1,5-a]pyrazin-7(8H)-yl)methanone (15.7 mg, 0.037 mmol) was separated by SFC separation ((DAICEL CHIRALCEL IG (250 × 30 mm, 10 μm); flow rate: 64 mL/min; gradient: 25% B over 4 min; mobile phase A: CO_2 , mobile phase B: $\text{MeOH}(0.1\%\text{NH}_3\text{H}_2\text{O})$) to afford a first eluted compound and a second eluted compound. First eluted compound (**Example 10A**): LC-MS: 384.1 $[M+H]^+$. ^1H NMR (400 MHz, CD_3OD) δ 7.71 – 7.55 (m, 1H), 7.44 – 7.29 (m, 2H), 7.11 – 7.01 (m, 1H), 6.94 – 6.65 (m, 1H), 5.68 – 5.10 (m, 1H), 5.03 – 4.48 (m, 2H), 3.91 – 3.39 (m, 1H), 1.66 – 1.46 (m, 3H). Second eluted compound (**Example 10B**): LC-MS: 384.1 $[M+H]^+$. ^1H NMR (400 MHz, CD_3OD) δ 7.66 – 7.46 (m, 1H), 7.40 – 7.21 (m, 2H), 7.07 – 6.94 (m, 1H), 6.90 – 6.53 (m, 1H), 5.58 – 5.03 (m, 1H), 4.96 – 4.46 (m, 2H), 3.81 – 3.38 (m, 1H), 1.55 – 1.42 (m, 3H). The absolute stereochemistry for the first and second eluted compounds was not determined.

Example 11: (4-Chloro-1H-benzo[d]imidazol-2-yl)(1-methyl-3,4-dihydro-2,6-naphthyridin-2(1H)-yl)methanone



[00196] Step A: To a solution of 1-(3-bromopyridin-4-yl)ethan-1-ol (5.00 g, 26.9 mmol) in THF (50.0 mL) was added MeMgBr (3M, 26.9 mL, 26.9 mmol) at -65 °C. The mixture was stirred at 0 °C for 3 h. The mixture was poured into NH₄Cl (70.0 mL) and extracted with EtOAc (70.0 mL x 3). The combined organic layers were concentrated under reduced pressure to give 1-(3-bromopyridin-4-yl)ethan-1-ol. LC-MS: 202.2 [M+H]⁺.

[00197] Step B: To a mixture of 1-(3-bromopyridin-4-yl)ethan-1-ol (2.60 g, 12.9 mmol) in DCM (26.0 mL) was added DHP (1.76 mL, 19.3 mmol) and TsOH (102 mg, 0.594 mmol). The mixture was stirred at 25 °C for 12 h. The mixture was poured into NaHCO₃ (26.0 mL) and extracted with DCM (20.0 mL x 3). The combined organic layers were dried over Na₂SO₄, filtered, and concentrated under vacuum to give a residue which was purified by flash silica gel chromatography using a gradient of EtOAc/petroleum ether from 1/100 to 1/10 to afford 3-bromo-4-(1-((tetrahydro-2H-pyran-2-yl)oxy)ethyl)pyridine. LC-MS: 286.1 [M+H]⁺.

[00198] Step C: A solution of 3-bromo-4-(1-((tetrahydro-2H-pyran-2-yl)oxy)ethyl)pyridine (750 mg, 2.62 mmol), (2-((tert-butoxycarbonyl)amino)ethyl)trifluoroborate (724 mg, 2.88 mmol), Pd(dppf)Cl₂ (62.5 mg, 0.085 mmol), Cs₂CO₃ (2.31 g, 7.08 mmol) in toluene (21.0 mL) and H₂O (7.00 mL) was degassed and purged with nitrogen for 3 times. The resulting mixture was stirred at 80 °C for 12 h under nitrogen atmosphere. The mixture was poured into H₂O (25.0 mL) and extracted with EtOAc (25.0 mL x 3). The combined organic layers were dried over Na₂SO₄, filtered, and concentrated under vacuum to give a residue which was purified by flash silica gel chromatography using a gradient of EtOAc/petroleum ether from 1/100 to 1/2 to afford *tert*-butyl (2-(4-(1-((tetrahydro-2H-pyran-2-yl)oxy)ethyl)pyridin-3-yl)ethyl)carbamate. LC-MS: 351.1 [M+H]⁺.

[00199] Step D: To a mixture of *tert*-butyl (2-(4-(1-((tetrahydro-2H-pyran-2-yl)oxy)ethyl)pyridin-3-yl)ethyl)carbamate (430 mg, 1.23 mmol) in MeOH (3.00 mL) was added

TsOH (317 mg, 1.84 mmol). The mixture was stirred at 25 °C for 2 h. The mixture was poured into NaHCO₃ (2.00 mL) and extracted with DCM (1.00 mL x 3). The combined organic layers were dried over Na₂SO₄, filtered, and concentrated under vacuum to give a residue which was purified by flash silica gel chromatography using a gradient of EtOAc/petroleum ether from 1/100 to 1/5 to afford *tert*-butyl (2-(4-(1-hydroxyethyl)pyridin-3-yl)ethyl)carbamate. LC-MS: 267.2 [M+H]⁺.

[00200] Step E: To a solution of *tert*-butyl (2-(4-(1-hydroxyethyl)pyridin-3-yl)ethyl)carbamate (50.0 mg, 0.188 mmol) in DCM (2.00 mL) was added TEA (28.5 mg, 0.281 mmol), followed by MsCl (27.9 mg, 0.244 mmol) at 0 °C. The mixture was stirred at 0 °C under nitrogen atmosphere. The mixture was poured into NaHCO₃ (5.00 mL) and extracted with DCM (2.00 mL x 3). The combined organic layers were dried over Na₂SO₄, filtered, and concentrated under vacuum to give 1-[3-[2-(*tert*-butoxycarbonylamino)ethyl]-4-pyridyl]ethyl methanesulfonate. ¹H NMR (400 MHz, CDCl₃) δ 8.79 – 8.64 (m, 2H), 8.10 – 8.00 (m, 1H), 6.42 – 6.28 (m, 1H), 5.24 – 5.05 (m, 1H), 3.69 (s, 3H), 3.55 – 3.49 (m, 1H), 3.39 – 3.32 (m, 1H), 1.44 (s, 3H), 1.41 (s, 9H).

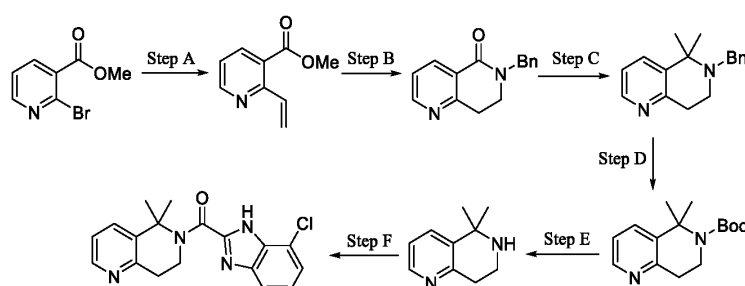
[00201] Step F: To a solution of 1-[3-[2-((*tert*-butoxycarbonyl)amino)ethyl]pyridin-4-yl]ethyl methanesulfonate (50.0 mg, 0.145 mmol) in DMF (1.00 mL) was added KI (2.41 mg, 0.014 mmol), followed by *t*-BuONa (27.9 mg, 0.290 mmol). The mixture was stirred at 100 °C for 30 min. The reaction mixture was allowed to cool to room temperature, poured into NaHCO₃ (5.00 mL) and extracted with Petroleum ether (2.00 mL x 2). The aqueous phase was adjusted to pH 4 with HCl (1M aqueous) and extracted with EtOAc (3.00 mL x 3). The combined organic layers were dried over Na₂SO₄ filtered, and concentrated under vacuum to give a residue which was purified by preparative TLC (Petroleum ether : Ethyl acetate = 1/1, R_f = 0.5) to afford *tert*-butyl 1-methyl-3,4-dihydro-2,6-naphthyridine-2(1*H*)-carboxylate. LC-MS: 249.2 [M+H]⁺. ¹H NMR (400 MHz, CDCl₃) δ 8.45 – 8.34 (m, 2H), 7.10 – 7.01 (m, 1H), 5.33 – 5.07 (m, 1H), 4.39 – 4.06 (m, 1H), 3.28 – 3.03 (m, 1H), 2.90 – 2.83 (m, 1H), 2.81 – 2.71 (m, 1H), 1.50 (s, 10H), 1.45 (d, *J* = 6.9 Hz, 3H).

[00202] Step G: To a solution of *tert*-butyl 1-methyl-3,4-dihydro-2,6-naphthyridine-2(1*H*)-carboxylate (20.0 mg, 0.080 mmol) in EtOAc (0.50 mL) was added HCl/EtOAc (4M, 0.4 mL). The mixture was stirred at 20 °C for 1 h. The mixture was concentrated under vacuum to give 1-methyl-1,2,3,4-tetrahydro-2,6-naphthyridine. LC-MS: 149.2 [M+H]⁺.

[00203] Step H: A mixture of 4-chloro-1*H*-benzo[*d*]imidazole-2-carboxylic acid (13.0 mg, 0.067 mmol), 1-methyl-1,2,3,4-tetrahydro-2,6-naphthyridine (10.0 mg, 0.067 mmol), HATU (25.7 mg, 0.067 mmol) and DIEA (17.4 mg, 0.135 mmol) in DMF (1.00 mL) was stirred at 20 °C for 2 h. The reaction mixture was poured into H₂O (1.00 mL) and extracted with EtOAc (0.50

mL x 3). The combined organic layers were dried over Na₂SO₄, filtered, and concentrated under vacuum to give a residue which was purified by preparative HPLC (Waters Xbridge C18 column (150 × 50 mm, 10 μm); flow rate: 60 mL/min; gradient: 25% – 55% B over 8 min; mobile phase A: 10mMNH₄HCO₃, mobile phase B: acetonitrile) to afford (4-chloro-1*H*-benzo[*d*]imidazol-2-yl)(1-methyl-3,4-dihydro-2,6-naphthyridin-2(1*H*)-yl)methanone. LC-MS: 327.1 [M+H]⁺. ¹H NMR (400 MHz, CDCl₃) δ 10.54 – 10.42 (m, 1H), 7.81 – 7.74 (m, 1H), 7.42 (br s, 2H), 7.35 – 7.28 (m, 2H), 6.59 – 6.32 (m, 1H), 5.91 – 4.96 (m, 1H), 3.76 – 3.55 (m, 1H), 3.35 – 3.24 (m, 1H), 3.21 – 3.01 (m, 2H), 1.67 (br d, *J* = 6.8 Hz, 3H).

Example 12: (7-Chloro-1*H*-benzo[*d*]imidazol-2-yl)(5,5-dimethyl-7,8-dihydro-1,6-naphthyridin-6(5*H*)-yl)methanone



[00204] Step A: To a mixture of methyl 2-bromopyridine-3-carboxylate (1.00 g, 4.63 mmol), 4,4,5,5-tetramethyl-2-vinyl-1,3,2-dioxaborolane (1.43 g, 9.26 mmol) and K₃PO₄ (2.95 g, 13.9 mmol) in THF (20.0 mL) and H₂O (4.00 mL) was added Pd(dppf)Cl₂ (677 mg, 0.926 mmol). The mixture was degassed and purged with nitrogen three times and stirred at 80 °C for 3 h under a nitrogen atmosphere. The reaction mixture was allowed to cool to room temperature, poured into water (20.0 mL) and extracted with EtOAc (20.0 mL x 5). The combined organic layers were dried over Na₂SO₄, filtered, and concentrated under vacuum to give a residue which was purified by flash silica gel chromatography using a gradient of EtOAc/petroleum ether from 0/1 to 1/5 to afford methyl 2-vinylnicotinate. LC-MS: 164.2 [M+H]⁺.

[00205] Step B: A solution of methyl 2-vinylnicotinate (400 mg, 2.46 mmol) and phenylmethanamine (1.31 g, 12.3 mmol) in DMF (8.00 mL) was stirred at 150 °C for 2 h under microwave. The reaction mixture was allowed to cool to room temperature, poured into water (10.0 mL) and extracted with EtOAc (10.0 mL x 5). The combined organic layers were dried over Na₂SO₄, filtered, and concentrated under vacuum to give a residue which was purified by flash silica gel chromatography using a gradient of EtOAc/petroleum ether from 0/1 to 1/1 to afford 6-benzyl-7,8-dihydro-1,6-naphthyridin-5(6*H*)-one. LC-MS: 286.1 [M+H]⁺.

[00206] Step C: To a solution of 6-benzyl-7,8-dihydro-1,6-naphthyridin-5(6*H*)-one (300 mg, 1.26 mmol) in THF (6.00 mL) was added ZrCl₄ (382 mg, 1.64 mmol). The mixture was degassed

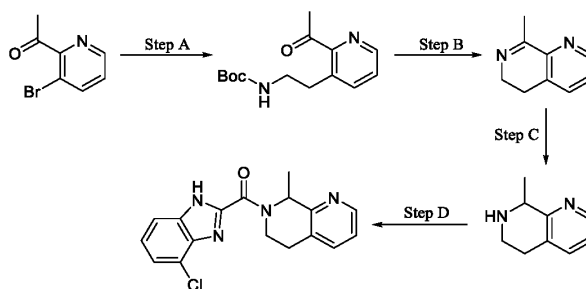
and purged with nitrogen three times and stirred at -10 °C for 0.5 h under a nitrogen atmosphere. Then MeMgBr (3M, 3.37 mL) was added and the mixture was stirred at 20 °C for 2 h. The reaction mixture was quenched with NH₄Cl (aqueous 10.0 mL) and extracted with EtOAc (3 x 3.00 mL). The combined organic layers were dried over Na₂SO₄, filtered, and concentrated under vacuum to give a residue which was purified by flash silica gel chromatography using a gradient of EtOAc/petroleum ether from 0/1 to 1/1 to afford 6-benzyl-5,5-dimethyl-5,6,7,8-tetrahydro-1,6-naphthyridine. LC-MS: 253.2 [M+H]⁺.

[00207] Step D: To a solution of palladium on carbon (10%, contains 67% water, 211 mg, 0.198 mmol) in MeOH (5.00 mL) was added 6-benzyl-5,5-dimethyl-5,6,7,8-tetrahydro-1,6-naphthyridine (50.0 mg, 0.198 mmol) and Boc₂O (47.6 mg, 0.218 mmol). The mixture was degassed and purged with hydrogen three times and stirred at 50 °C for 1 h under hydrogen (50 Psi). The reaction mixture was filtered through a pad of Celite and the filtrate was concentrated under vacuum to give a residue which was purified by preparative TLC (EtOAc/petroleum ether = 1/3, R_f = 0.55) to afford tert-butyl 5,5-dimethyl-7,8-dihydro-1,6-naphthyridine-6(5H)-carboxylate. LC-MS: 253.2 [M+H]⁺.

[00208] Step E: To a solution of tert-butyl 5,5-dimethyl-7,8-dihydro-1,6-naphthyridine-6(5H)-carboxylate (20.0 mg, 0.076 mmol) in EtOAc (1.00 mL) was added HCl/EtOAc (4M, 4.00 mL). The resulting mixture was stirred at 20 °C for 1 h. The mixture was concentrated under vacuum at 30 °C to give 5,5-dimethyl-5,6,7,8-tetrahydro-1,6-naphthyridine. LC-MS: 163.1 [M+H]⁺.

[00209] Step F: A mixture of 7-chloro-1H-benzo[d]imidazole-2-carboxylic acid (9.89 mg, 0.050 mmol), 5,5-dimethyl-5,6,7,8-tetrahydro-1,6-naphthyridine (10.0 mg, 0.050 mmol), HATU (9.57 mg, 0.025 mmol) and DIEA (19.5 mg, 0.151 mmol) in DMF (0.50 mL) was stirred at 20 °C for 1 h. The reaction mixture was poured into H₂O (2.00 mL) and extracted with EtOAc (3.00 mL x 3). The combined organic layers were dried over Na₂SO₄, filtered, and concentrated under vacuum to give a residue which was purified by preparative HPLC (Phenomenex Luna C18 column (75 × 30 mm, 3 μm); flow rate: 25 mL/min; gradient: 5% – 35% B over 8 min; mobile phase A: 0.04% aqueous HCl, mobile phase B: acetonitrile) to afford (7-chloro-1H-benzo[d]imidazol-2-yl)(5,5-dimethyl-7,8-dihydro-1,6-naphthyridin-6(5H)-yl)methanone. LC-MS: 241.1 [M+H]⁺. ¹H NMR (400 MHz, DMSO-*d*₆) δ 8.78 – 8.54 (m, 2H), 7.91 – 7.79 (m, 1H), 7.56 (d, *J* = 7.9 Hz, 1H), 7.42 – 7.23 (m, 2H), 4.21 (br d, *J* = 5.1 Hz, 2H), 3.34 (br t, *J* = 4.8 Hz, 2H), 1.93 (s, 6H).

Example 13: (4-Chloro-1H-benzo[d]imidazol-2-yl)(8-methyl-5,8-dihydro-1,7-naphthyridin-7(6H)-yl)methanone



[00210] Step A: 1-(3-Bromopyridin-2-yl)ethan-1-one (200 mg, 1.00 mmol), (2-((tert-butoxycarbonyl)amino)ethyl)trifluoroborate (301 mg, 1.20 mmol) were dissolved in H₂O (3.00 mL) and toluene (9.00 mL) at room temperature under nitrogen. Pd(dppf)Cl₂ (20.0 mg, 0.027 mmol) and then Cs₂CO₃ (977 mg, 3.00 mmol) were added. The mixture was heated at 80 °C for 5 h and then cooled to room temperature. The reaction mixture was poured into H₂O (10.0 mL) and extracted with EtOAc (10.0 mL x 2). The combined organic layers were dried over Na₂SO₄, filtered, and concentrated under vacuum to give a residue which was purified by flash chromatography on silica gel using a gradient of EtOAc/petroleum ether from 0/100 to 1/10 to afford *tert*-butyl (2-(2-acetylpyridin-3-yl)ethyl)carbamate. LC-MS: 265.3 [M+H]⁺.

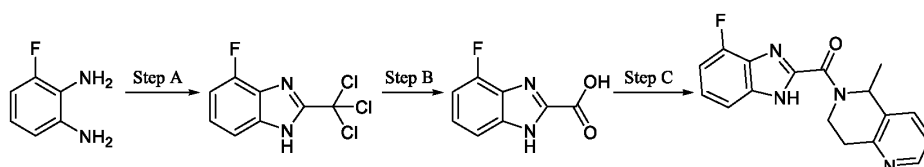
[00211] Step B: *tert*-Butyl (2-(2-acetylpyridin-3-yl)ethyl)carbamate (80.0 mg, 0.303 mmol) was dissolved in EtOAc (1.00 mL) and then HCl/EtOAc (4M, 1.00 mL) was added. The mixture was stirred at room temperature for 1 h. The reaction mixture was concentrated under vacuum to give 8-methyl-5,6-dihydro-1,7-naphthyridine. LC-MS: 147.2 [M+H]⁺.

[00212] Step C: 8-Methyl-5,6-dihydro-1,7-naphthyridine (40.0 mg, 0.274 mmol) was dissolved in MeOH (2.00 mL) and then NaBH₃CN (25.8 mg, 0.410 mmol) was added. The mixture was stirred at room temperature for 1 h. The reaction mixture was poured into H₂O (2.00 mL) and extracted with DCM (1.00 mL x 3). The combined organic layers were dried over Na₂SO₄, filtered, and concentrated under vacuum to give 8-methyl-5,6,7,8-tetrahydro-1,7-naphthyridine. LC-MS: 149.2 [M+H]⁺.

[00213] Step D: 8-Methyl-5,6,7,8-tetrahydro-1,7-naphthyridine (20.0 mg, 0.135 mmol), 4-chloro-1H-benzo[d]imidazole-2-carboxylic acid (26.5 mg, 0.135 mmol), HATU (25.7 mg, 0.0675 mmol) and DIEA (24.0 µL, 0.135 mmol) were dissolved in DMF (1.00 mL) and stirred at room temperature for 1 h. The reaction mixture was poured into H₂O (1.00 mL) and extracted with EtOAc (1.00 mL x 3). The combined organic layers were dried over Na₂SO₄, filtered, and concentrated under vacuum to give a residue which was purified by preparative HPLC (Phenomenex Luna C18 column (100 × 40 mm, 5 µm); flow rate: 60 mL/min; gradient: 10% – 40% B over 8 min; mobile phase A: 0.1% aqueous TFA, mobile phase B: acetonitrile). The relevant fractions were lyophilized to afford (4-chloro-1H-benzo[d]imidazol-2-yl)(8-methyl-5,8-

dihydro-1,7-naphthyridin-7(6H)-yl)methanone. LC-MS: 327.1 $[M+H]^+$. 1H NMR (400 MHz, DMSO- d_6) δ 13.50 (br s, 1H), 8.47 (br dd, J = 3.9, 17.9 Hz, 1H), 7.78 - 7.65 (m, 1H), 7.59 - 7.46 (m, 1H), 7.42 - 7.36 (m, 1H), 7.35 - 7.26 (m, 2H), 5.68 - 5.39 (m, 1H), 3.29 (br d, J = 5.0 Hz, 2H), 3.02 (br s, 2H), 1.73 (br d, J = 6.8 Hz, 3H).

Example 14: (4-Fluoro-1H-benzo[d]imidazol-2-yl)(5-methyl-7,8-dihydro-1,6-naphthyridin-6(5H)-yl)methanone



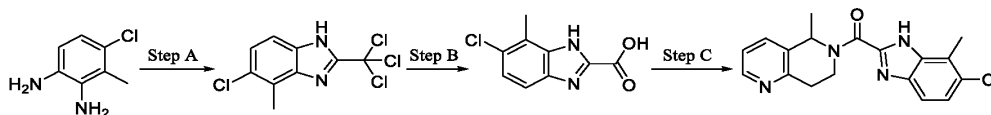
[00214] Step A: A solution of 3-fluorobenzene-1,2-diamine (1.00 g, 7.93 mmol) and methyl 2,2,2-trichloroacetimidate (1.40 g, 7.93 mmol) in AcOH (8.00 mL) was stirred at 25 °C for 3 h. The reaction mixture was filtered and the filter cake was washed with H₂O (5.00 mL) and dried in vacuum to give 4-fluoro-2-(trichloromethyl)-1H-benzo[d]imidazole which was used in the next step without any further purification. LC-MS: 253.0 $[M+H]^+$.

[00215] Step B: A solution of 4-fluoro-2-(trichloromethyl)-1H-benzo[d]imidazole (2.00 g, 7.90 mmol) in NaOH aqueous (2M, 40 mL) was stirred at 20 °C for 1 h. The reaction mixture was poured into H₂O (25.0 mL), extracted with MTBE (20.0 mL x 2). The combined organic layers were discarded. The water phase was adjusted pH 7 by using HCl aqueous (1M) and lyophilized further to give a residue. The residue was washed with DCM (10.0 mL x 2) and filtered. The combined filtrates layers were dried over Na₂SO₄ and concentrated under vacuum to give 4-fluoro-1H-benzo[d]imidazole-2-carboxylic acid which was used in the next step without any further purification. LC-MS: 181.2 $[M+H]^+$.

[00216] Step C: To a solution of 4-fluoro-1H-benzo[d]imidazole-2-carboxylic acid (20.0 mg, 0.111 mmol) and 5-methyl-5,6,7,8-tetrahydro-1,6-naphthyridine (16.5 mg, 0.111 mmol) in DMF (1.00 mL) was added HATU (42.2 mg, 0.111 mmol) and DIEA (14.3 mg, 0.111 mmol). The mixture was stirred at 25 °C for 3 h. The mixture was poured into H₂O (1.00 mL) and extracted with EtOAc (1.00 mL x 2). The combined organic layers were dried over Na₂SO₄, filtered and concentrated under vacuum to give a residue which was purified by preparative HPLC (Waters Xbridge BEH C18 column (100 x 30 mm, 10 μ m); flow rate: 25 mL/min; gradient: 25% – 60% B over 8 min; mobile phase A: 10 mM aqueous NH₄HCO₃, mobile phase B: acetonitrile) to afford (4-fluoro-1H-benzo[d]imidazol-2-yl)(5-methyl-7,8-dihydro-1,6-naphthyridin-6(5H)-yl)methanone. LC-MS: 311.1 $[M+H]^+$. 1H NMR (400 MHz, CD₃OD) δ 10.51 (br s, 1H), 8.57 –

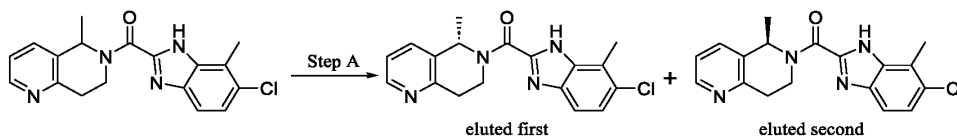
8.46 (m, 1H), 7.78 – 7.60 (m, 1H), 7.33 (br s, 2H), 7.14 – 7.01 (m, 1H), 6.55 – 5.84 (m, 1H), 3.87 – 3.68 (m, 1H), 3.48 – 3.18 (m, 3H), 1.90 – 1.67 (m, 3H).

Example 15: (6-Chloro-7-methyl-1H-benzimidazol-2-yl)-(5-methyl-7,8-dihydro-5H-1,6-naphthyridin-6-yl)methanone



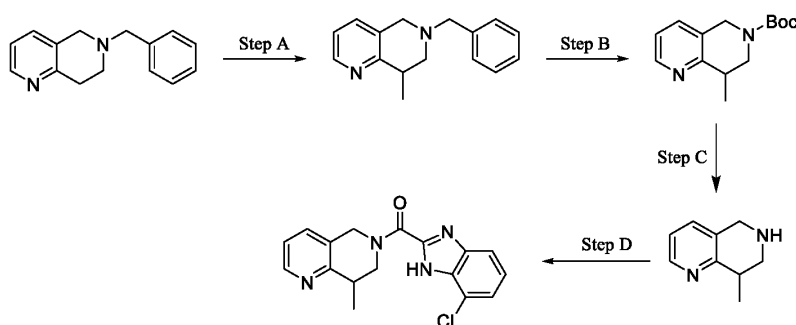
[00217] The title compound was prepared from 4-chloro-3-methylbenzene-1,2-diamine according to the procedure of Example 14, Steps A, B, and C. LC-MS: 341.1 [M+H]⁺. ¹H NMR (400 MHz, CDCl₃) δ 10.64 – 10.29 (m, 1H), 8.55 – 8.42 (m, 1H), 7.65 – 7.53 (m, 1H), 7.38 – 7.28 (m, 1H), 7.27 – 7.18 (m, 2H), 6.50 – 4.77 (m, 1H), 3.76 (dt, *J* = 3.8, 13.0 Hz, 1H), 3.53 – 3.06 (m, 3H), 2.81 – 2.53 (m, 3H), 1.79 (br dd, *J* = 6.4, 12.5 Hz, 1H), 1.65 (s, 2H).

Examples 15A and 15B: (R)-(6-Chloro-7-methyl-1H-benzo[d]imidazol-2-yl)(5-methyl-7,8-dihydro-1,6-naphthyridin-6(5H)-yl)methanone and (S)-(6-Chloro-7-methyl-1H-benzo[d]imidazol-2-yl)(5-methyl-7,8-dihydro-1,6-naphthyridin-6(5H)-yl)methanone



[00218] **Step A:** (6-Chloro-7-methyl-1H-benzo[d]imidazol-2-yl)(5-methyl-7,8-dihydro-1,6-naphthyridin-6(5H)-yl)methanone (40.0 mg, 0.120 mmol) was separated by SFC separation (Phenomenex-CHIRALPAK IH (250 × 30 mm, 10 μm); flow rate: 30 mL/min; gradient: 42% B over 14 min; mobile phase A: heptane, mobile phase B: EtOH(0.1% NH₃H₂O) to afford a first eluted compound and a second eluted compound. First eluted compound (**Example 15B**): LC-MS: 340.9 [M+H]⁺. ¹H NMR (400 MHz, CDCl₃) δ 10.22 (br dd, *J* = 4.4, 7.6 Hz, 1H), 8.51 – 8.23 (m, 1H), 7.59 – 7.21 (m, 3H), 7.16 – 7.08 (m, 1H), 6.44 – 5.67 (m, 1H), 5.09 – 3.59 (m, 1H), 3.45 – 2.91 (m, 3H), 2.72 – 2.40 (m, 3H), 1.73 – 1.55 (m, 3H). Second eluted compound (**Example 15A**): LC-MS: 340.9 [M+H]⁺. ¹H NMR (400 MHz, CDCl₃) δ 10.52 – 10.21 (m, 1H), 8.55 – 8.42 (m, 1H), 7.69 – 7.29 (m, 3H), 7.27 – 7.15 (m, 1H), 6.53 – 5.75 (m, 1H), 5.09 – 3.67 (m, 1H), 3.53 – 3.01 (m, 3H), 2.79 – 2.52 (m, 3H), 1.84 – 1.63 (m, 3H).

Example 16: (7-Chloro-1H-benzo[d]imidazol-2-yl)(8-methyl-7,8-dihydro-1,6-naphthyridin-6(5H)-yl)methanone



[00219] Step A: To a solution of diisopropylamine (1.17 g, 11.6 mmol) in THF (7.00 mL) was added dropwise *n*-BuLi (2.5 M in THF, 1.39 mL) at -78 °C over 0.5 h under nitrogen. Then a solution of 6-benzyl-5,6,7,8-tetrahydro-1,6-naphthyridine (650 mg, 2.90 mmol) in THF (14.0 mL) was added dropwise. After stirring for 1 h, MeI (6.17 g, 43.5 mmol) was added dropwise at -78 °C. The resulting mixture was stirred at -78 °C for 1 h. Dropped 2.00 mL of MeOH into the system, then the reaction mixture was poured into H₂O (10.0 mL) and extracted with EtOAc (10.0 mL x 3). The combined organic layers were dried over Na₂SO₄, filtered, and concentrated under vacuum to give a residue which was purified by flash silica gel chromatography using a gradient of EtOAc/petroleum ether from 0/100 to 1/4 to afford 6-benzyl-8-methyl-5,6,7,8-tetrahydro-1,6-naphthyridine. LC-MS: 239.1 [M+H]⁺.

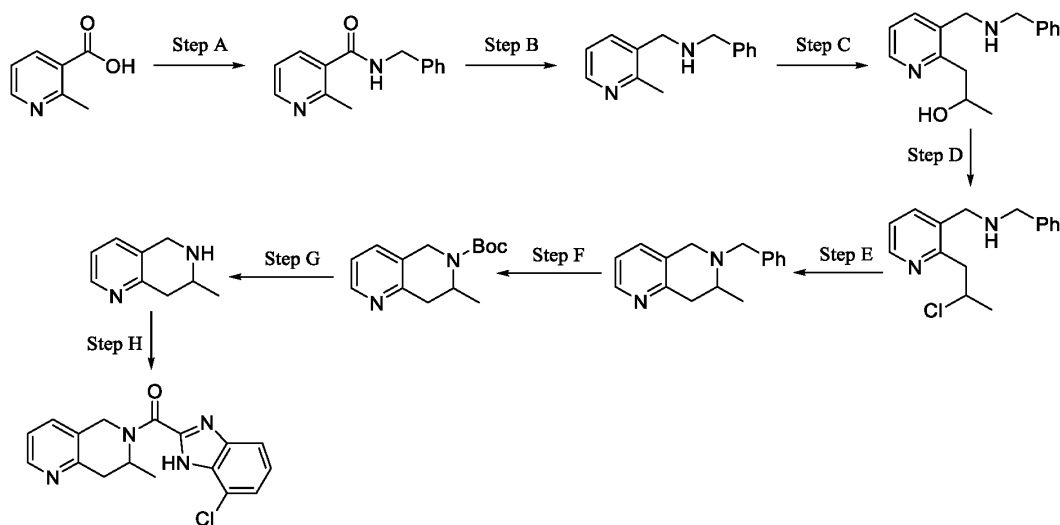
[00220] Step B: To a solution of 6-benzyl-8-methyl-5,6,7,8-tetrahydro-1,6-naphthyridine (400 mg, 1.68 mmol) in MeOH (20.0 mL) was added palladium on carbon (10%, contains 67% water, 1.79 g) and Boc₂O (203 mg, 1.85 mmol). The mixture was stirred at 25 °C for 2 h under hydrogen (50 Psi). The mixture was filtered through Celite pad, then the solvent was removed to give tert-butyl 8-methyl-7,8-dihydro-1,6-naphthyridine-6(5H)-carboxylate. LC-MS: 249.3 [M+H]⁺.

[00221] Step C: To a solution of tert-butyl 8-methyl-7,8-dihydro-1,6-naphthyridine-6(5H)-carboxylate (350 mg, 1.41 mmol) in EtOAc (2.00 mL) was added HCl/EtOAc (4M, 10.0 mL). The mixture was stirred at 20 °C for 1 h. The mixture was concentrated under vacuum to give 8-methyl-5,6,7,8-tetrahydro-1,6-naphthyridine. LC-MS: 149.1 [M+H]⁺.

[00222] Step D: To a solution of 8-methyl-5,6,7,8-tetrahydro-1,6-naphthyridine (8.00 mg, 0.043 mmol), 7-chloro-1H-benzo[d]imidazole-2-carboxylic acid (8.52 mg, 0.043 mmol) in DMF (0.50 mL) was added DIEA (11.2 mg, 0.087 mmol) and HATU (8.24 mg, 0.022 mmol). The mixture was stirred at 20 °C for 1 h. The mixture was treated with H₂O (2.00 mL) and extracted with EtOAc (3.00 mL x 3). The combined organic layers were dried over Na₂SO₄, filtered, and concentrated under vacuum to give a residue which was purified by preparative HPLC (Phenomenex Luna C18 column (75×30 mm, 3 μm); flow rate: 25 mL/min; gradient: 10% –

40% B over 8 min; mobile phase A: 0.04% aqueous HCl, mobile phase B: acetonitrile) for second time to afford (7-chloro-1H-benzo[d]imidazol-2-yl)(8-methyl-7,8-dihydro-1,6-naphthyridin-6(5H)-yl)methanone. LC-MS: 327.1 $[M+H]^+$. 1H NMR (400 MHz, MeOD) δ 8.73 (br d, $J = 4.5$ Hz, 1H), 8.62 – 8.44 (m, 1H), 8.07 – 7.87 (m, 1H), 7.59 (br d, $J = 7.9$ Hz, 1H), 7.43 – 7.27 (m, 2H), 6.52 – 5.31 (m, 2H), 4.63 – 4.30 (m, 1H), 4.06 – 3.49 (m, 2H), 1.60 – 1.49 (m, 3H).

Example 17: (7-Chloro-1H-benzimidazol-2-yl)-(7-methyl-7,8-dihydro-5H-1,6-naphthyridin-6-yl)methanone



[00223] Step A: To a solution of 2-methylnicotinic acid (2.00 g, 14.6 mmol) and phenylmethanamine (1.56 g, 14.6 mmol) in DMF (10.0 mL) was added DIEA (5.65 g, 43.7 mmol) and HATU (11.1 g, 29.2 mmol). The mixture was stirred at 20 °C for 1 h. The mixture was treated with H₂O (15.0 mL) and extracted with EtOAc (15.0 mL x 3). The combined organic layers were dried over Na₂SO₄, filtered, and concentrated under vacuum to give a residue, which was purified by flash silica gel chromatography using a gradient of EtOAc/petroleum ether from 1/100 to 2/5 to afford N-benzyl-2-methyl-pyridine-3-carboxamide. LC-MS: 227.1 $[M+H]^+$.

[00224] Step B: To a solution of N-benzyl-2-methyl-pyridine-3-carboxamide (500 mg, 2.21 mmol) in THF (5.50 mL) was added dropwise BH₃.THF (1M, 11.0 mL) at 0 °C. The mixture was stirred at 70 °C for 2 h. To the mixture was added MeOH dropwise at 0 °C and then refluxed for 1 h. The resulting mixture was concentrated under vacuum to give a residue, which was purified by flash silica gel chromatography using a gradient of EtOAc/petroleum ether from 1/100 to 1/2 to afford N-benzyl-1-(2-methylpyridin-3-yl)methanamine. LC-MS: 213.3 $[M+H]^+$.

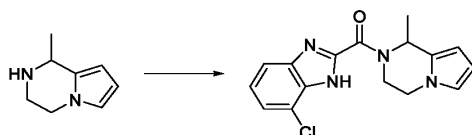
[00225] Step C: A mixture of diisopropylamine (357 mg, 3.53 mmol) in THF (10.0 mL) was degassed and purged with nitrogen for 3 times, and then n-BuLi (1.5 M, 1.88 mL) was added at -

70 °C during a period of 10 min. N-benzyl-1-(2-methylpyridin-3-yl)methanamine (250 mg, 1.18 mmol) in THF (2.50 mL) was then added into the solution dropwise at -70 °C for 1h. Then acetaldehyde (5M, 1.18 mL) was added. The mixture was stirred at -70 °C for 1 h under nitrogen atmosphere. The reaction mixture was poured into saturated NH₄Cl aqueous (5.00 ml), extracted with EtOAc (10.0 ml x 3). The combined organic layers were dried over Na₂SO₄, filtered and concentrated under vacuum to give a residue, which was purified by flash silica gel chromatography using a gradient of EtOAc/petroleum ether from 1/100 to 1/2 to afford 1-(3-((benzylamino)methyl)pyridin-2-yl)propan-2-ol. LC-MS: 257.3 [M+H]⁺.

[00226] Step D: To a solution of 1-(3-((benzylamino)methyl)pyridin-2-yl)propan-2-ol (50.0 mg, 0.195 mmol) in CHCl₃ (0.50 mL) was added SOCl₂ (69.0 mg, 0.585 mmol) at 0 °C. Then the mixture was stirred at 70 °C for 2 h. The reaction mixture was poured into saturated aqueous NaHCO₃ (5.00ml) and extracted with DCM (5.00 ml x 3). The combined organic layers were dried over Na₂SO₄, filtered and concentrated under vacuum to give N-benzyl-1-(2-(2-chloropropyl)pyridin-3-yl)methanamine. LC-MS: 275.3 [M+H]⁺.

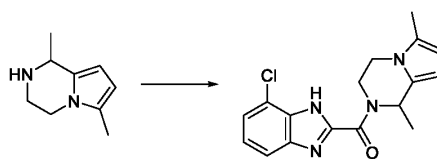
[00227] Steps E, F, and G: The title compound was prepared from N-benzyl-1-(2-(2-chloropropyl)pyridin-3-yl)methanamine according to the procedure of Example 16, Steps B, C, and D. LC-MS: 327.1 [M+H]⁺. ¹H NMR (400 MHz, CDCl₃) δ 10.69 – 10.31 (m, 1H), 8.51 (br t, *J* = 5.6 Hz, 1H), 7.82 – 7.52 (m, 1H), 7.48 – 7.28 (m, 2H), 7.24 – 7.16 (m, 1H), 6.91 – 6.63 (m, 1H), 5.55 – 5.35 (m, 1H), 5.06 – 4.45 (m, 1H), 3.64 – 3.29 (m, 1H), 3.10 – 2.83 (m, 1H), 1.42 – 1.24 (m, 4H).

Example 18: (7-Chloro-1H-benzo[d]imidazol-2-yl)(1-methyl-3,4-dihydropyrrolo[1,2-a]pyrazin-2(1H)-yl)methanone



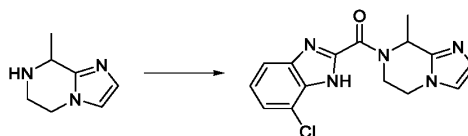
[00228] The title compound was prepared from 1-methyl-1,2,3,4-tetrahydropyrrolo[1,2-a]pyrazine and 7-chloro-1H-benzimidazole-2-carboxylic acid according to the procedure of Example 1, Step A. LC-MS: 315.1 [M+H]⁺. ¹H NMR (400 MHz, MeOD) δ 7.62 (d, *J* = 7.9 Hz, 1H), 7.44 – 7.33 (m, 3H), 6.39 – 6.05 (m, 1H), 5.81 (br d, *J* = 6.4 Hz, 1H), 5.32 (br d, *J* = 14.0 Hz, 1H), 4.14 (br d, *J* = 5.5 Hz, 2H), 3.92 – 3.55 (m, 2H), 1.59 (br d, *J* = 6.0 Hz, 3H).

Example 19: (7-Chloro-1H-benzo[d]imidazol-2-yl)(1,6-dimethyl-3,4-dihydropyrrolo[1,2-a]pyrazin-2(1H)-yl)methanone



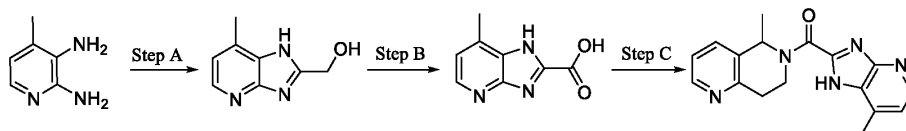
[00229] The title compound was prepared from 1,6-dimethyl-1,2,3,4-tetrahydropyrrolo[1,2-a]pyrazine and 7-chloro-1H-benzimidazole-2-carboxylic acid according to the procedure of Example 1, Step A. LC-MS: 329.3 [M+H]⁺. ¹H NMR (400 MHz, DMSO-*d*₆) δ 13.74 – 13.32 (m, 1H), 7.67 – 7.50 (m, 1H), 7.44 – 7.24 (m, 2H), 5.93 – 5.58 (m, 3H), 4.16 – 3.95 (m, 1H), 3.92 – 3.67 (m, 2H), 3.58 – 3.38 (m, 1H), 2.14 (s, 3H), 1.69 – 1.41 (m, 3H).

Example 20: (7-Chloro-1H-benzo[d]imidazol-2-yl)(8-methyl-5,6-dihydroimidazo[1,2-a]pyrazin-7(8H)-yl)methanone



[00230] The title compound was prepared from 8-methyl-5,6,7,8-tetrahydroimidazo[1,2-a]pyrazine and 7-chloro-1H-benzimidazole-2-carboxylic acid according to the procedure of Example 1, Step A. LC-MS: 316.3 [M+H]⁺. ¹H NMR (400 MHz, DMSO-*d*₆) δ 13.60 (br s, 1H), 7.54 (br s, 1H), 7.44 – 7.29 (m, 2H), 7.19 – 7.06 (m, 1H), 6.94 – 6.72 (m, 1H), 5.68 (q, *J* = 6.8 Hz, 1H), 4.31 – 3.96 (m, 2H), 3.91 – 3.48 (m, 1H), 3.33 (s, 2H), 1.74 – 1.49 (m, 3H).

Example 21: (7-Methyl-1H-imidazo[4,5-b]pyridin-2-yl)(5-methyl-7,8-dihydro-1,6-naphthyridin-6(5H)-yl)methanone



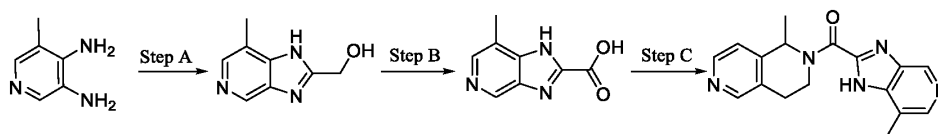
[00231] Step A: A solution of 4-methylpyridine-2,3-diamine (200 mg, 1.62 mmol) in 2-hydroxyacetic acid (247 mg, 3.25 mmol) was stirred at 150 °C for 3 h. The mixture was cooled down to room temperature, then treated with NaHCO₃ solution until some solid appeared. The mixture was filtered and the filter cake was dried in vacuum to give (7-methyl-1H-imidazo[4,5-b]pyridin-2-yl)methanol. LC-MS: 162.2 [M+H]⁺.

[00232] Step B: A solution of KMnO₄ (58.0 mg, 0.367 mmol) in H₂O (4.00 mL) was stirred at 100 °C. Then a mixture of (7-methyl-1H-imidazo[4,5-b]pyridin-2-yl)methanol (40.0 mg, 0.245 mmol) and Na₂CO₃ (19.0 mg, 179 mmol) in H₂O (4.00 mL) was added. The mixture was stirred at 100 °C for 2 h. The mixture was filtered and the filtrate was acidified to pH 2 – 3 with (1M

HCl). The resulting precipitate was filtered off and the cake was dried in vacuum to afford 7-methyl-1H-imidazo[4,5-b]pyridine-2-carboxylic acid. LC-MS: 176.1 [M+H]⁺.

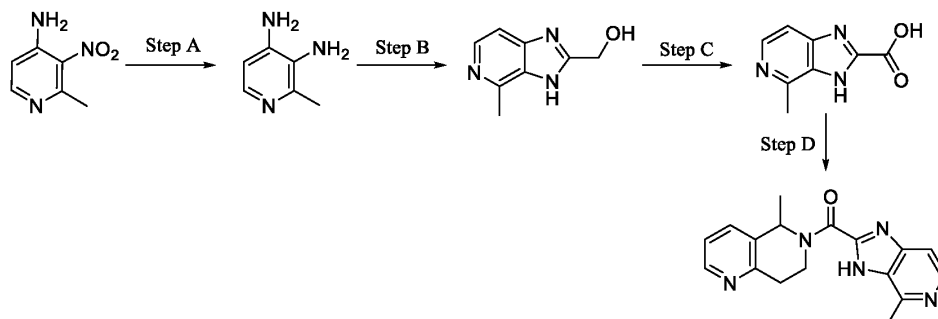
[00233] Step C: A mixture of 5-methyl-5,6,7,8-tetrahydro-1,6-naphthyridine (12.0 mg, 0.084 mmol), 7-methyl-1H-imidazo[4,5-b]pyridine-2-carboxylic acid (15.0 mg, 0.084 mmol), HATU (16.0 mg, 0.042 mmol) and DIEA (32.0 mg, 0.254 mmol) in DMF (0.500 mL) was stirred at 20 °C for 1 h. The reaction mixture was poured into H₂O (5.00 mL) and extracted with EtOAc (5.00 mL x 3). The combined organic layers were dried over Na₂SO₄, filtered, and concentrated under vacuum to give a residue which was purified by preparative HPLC (Phenomenex Luna C18 column 100 × 40 mm × 5 μm); flow rate: 25 mL/min; gradient: 1% – 18% B over 8 min; mobile phase A: 0.04% aqueous HCl, mobile phase B: acetonitrile) to afford (7-methyl-1H-imidazo[4,5-b]pyridin-2-yl)(5-methyl-7,8-dihydro-1,6-naphthyridin-6(5H)-yl)methanone. LC-MS: 308.2 [M+H]⁺. ¹H NMR (400 MHz, DMSO-*d*₆) δ 8.79 – 8.70 (m, 1H), 8.63 – 8.34 (m, 2H), 7.99 – 7.75 (m, 1H), 7.59 – 7.34 (m, 1H), 6.52 – 5.85 (m, 1H), 5.44 – 4.63 (m, 1H), 3.79 – 3.11 (m, 3H), 2.82 – 2.60 (m, 3H), 1.86 – 1.52 (m, 3H).

Example 22: (7-Methyl-1H-imidazo[4,5-c]pyridin-2-yl)(1-methyl-3,4-dihydro-2,6-naphthyridin-2(1H)-yl)methanone



[00234] The title compound was prepared from 5-methylpyridine-3,4-diamine according to the procedure of Example 21, Steps A, B, and C. LC-MS: 308.1 [M+H]⁺. ¹H NMR (400 MHz, CDCl₃) δ 10.75 – 10.54 (m, 1H), 9.09 (br s, 1H), 8.56 – 8.27 (m, 2H), 7.62 – 7.51 (m, 1H), 7.24 – 7.12 (m, 1H), 6.50 – 5.73 (m, 1H), 5.12 – 3.68 (m, 1H), 3.60 – 2.89 (m, 3H), 2.80 – 2.42 (m, 3H), 1.84 – 1.63 (m, 3H).

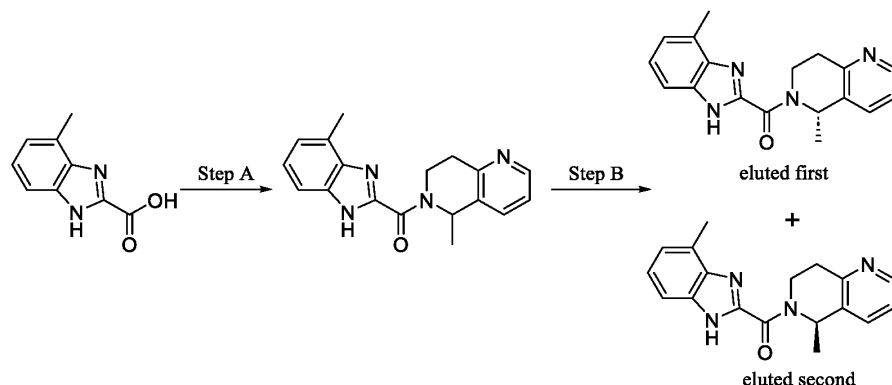
Example 23: (4-Methyl-3H-imidazo[4,5-c]pyridin-2-yl)(5-methyl-7,8-dihydro-1,6-naphthyridin-6(5H)-yl)methanone



[00235] Step A: A solution of 2-methyl-3-nitropyridin-4-amine (800 mg, 5.22 mmol) and Raney Ni (306 mg) in MeOH (8.00 mL) was degassed and purged with hydrogen for three times. The mixture was stirred at 20 °C for 1 h under hydrogen (15 psi). The suspension was filtered through a pad of Celite, and the filter cake was washed with EtOAc (2.00 mL × 3). The combined filtrates were concentrated under vacuum to give 2-methylpyridine-3,4-diamine. LC-MS: 124.2 [M+H]⁺.

[00236] Steps B, C, and D: The title compound was prepared from 2-methylpyridine-3,4-diamine according to the procedure of Example 21, Steps A, B, and C. LC-MS: 308.1 [M+H]⁺. ¹H NMR (400 MHz, CDCl₃) δ 8.57 – 8.33 (m, 1H), 7.64 – 7.43 (m, 1H), 7.37 – 7.28 (m, 1H), 7.26 – 7.02 (m, 3H), 3.35 – 2.79 (m, 4H), 2.33 – 2.08 (m, 1H), 1.88 – 1.57 (m, 3H), 1.48 – 0.73 (m, 3H).

Examples 24A and 24B: (S)-(4-Methyl-1H-benzo[d]imidazol-2-yl)(5-methyl-7,8-dihydro-1,6-naphthyridin-6(5H)-yl)methanone (Example 24A) and (R)-(4-methyl-1H-benzo[d]imidazol-2-yl)(5-methyl-7,8-dihydro-1,6-naphthyridin-6(5H)-yl)methanone (Example 24B)

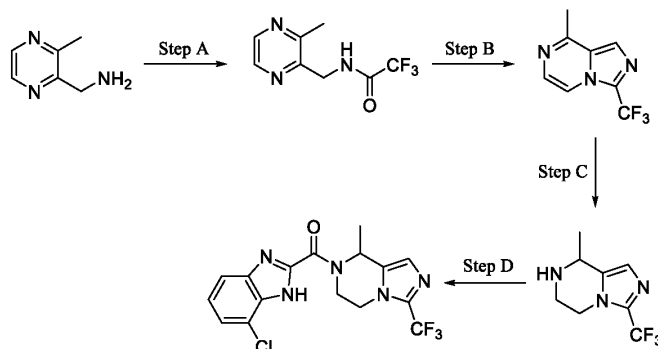


[00237] Step A: Racemic (4-methyl-1H-benzo[d]imidazol-2-yl)(5-methyl-7,8-dihydro-1,6-naphthyridin-6(5H)-yl)methanone was prepared from 5-methyl-5,6,7,8-tetrahydro-1,6-naphthyridine and 4-methyl-1H-benzo[d]imidazole-2-carboxylic acid according to the procedure of Example 1, Step A. LC-MS: 307.3 [M+H]⁺.

[00238] Step B: Racemic (4-methyl-1H-benzo[d]imidazol-2-yl)(5-methyl-7,8-dihydro-1,6-naphthyridin-6(5H)-yl)methanone (36.7 mg, 0.120 mmol) was separated by SFC separation ((Phenomenex-Cellulose-2(250 × 30 mm, 10 μm); flow rate: 70 mL/min; gradient: 45 – 45% B over 11 min; mobile phase A: CO₂, mobile phase B: IPA(0.1%NH₃H₂O)) to afford a first eluted compound and a second eluted compound. First eluted compound (**Example 24A**): LC-MS: 307.1 [M+H]⁺. ¹H NMR (400 MHz, CDCl₃) δ 10.61 (br s, 1H), 8.56 – 8.35 (m, 1H), 7.73 – 7.51

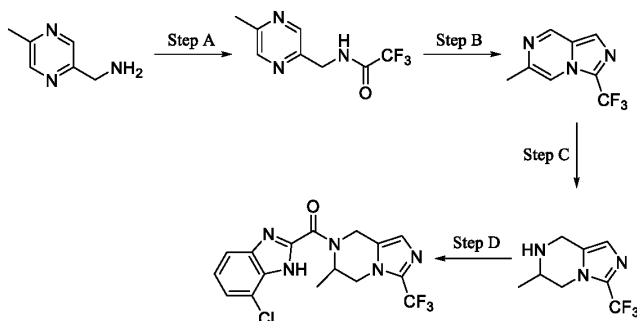
(m, 1H), 7.41 – 7.27 (m, 1H), 7.26 – 6.99 (m, 3H), 6.61 – 4.89 (m, 2H), 3.88 – 2.98 (m, 3H), 2.78 – 2.48 (m, 3H), 1.81 – 1.63 (m, 3H). Second eluted compound (**Example 24B**): LC-MS: 307.1 [M+H]⁺. ¹H NMR (400 MHz, CDCl₃) δ 10.38 (br d, *J* = 5.1 Hz, 1H), 8.61 – 8.32 (m, 1H), 7.82 – 7.47 (m, 1H), 7.43 – 7.28 (m, 1H), 7.26 – 7.06 (m, 3H), 6.65 – 4.81 (m, 2H), 3.83 – 3.05 (m, 3H), 2.80 – 2.46 (m, 3H), 1.89 – 1.60 (m, 3H).

Example 25: (7-Chloro-1H-benzo[d]imidazol-2-yl)(8-methyl-3-(trifluoromethyl)-5,6-dihydroimidazo[1,5-a]pyrazin-7(8H)-yl)methanone



[00239] The title compound was prepared from 4-chloro-3-methylbenzene-1,2-diamine according to the procedure of Example 10, Steps C, D, E, and F. LC-MS: 384.1 [M+H]⁺. ¹H NMR (400 MHz, CDCl₃) δ 10.77 – 10.40 (m, 1H), 7.81 – 7.29 (m, 3H), 7.08 – 7.00 (m, 1H), 6.83 – 6.58 (m, 1H), 6.14 – 5.02 (m, 1H), 4.57 – 3.42 (m, 3H), 1.90 – 1.61 (m, 3H).

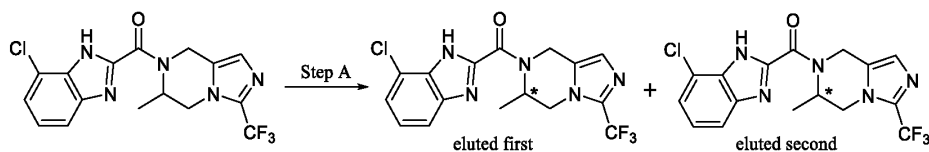
Example 26: (7-Chloro-1H-benzo[d]imidazol-2-yl)(6-methyl-3-(trifluoromethyl)-5,6-dihydroimidazo[1,5-a]pyrazin-7(8H)-yl)methanone



[00240] The title compound was prepared from (5-methylpyrazin-2-yl)methanamine according to the procedure of Example 10, Steps C, D, E, and F. LC-MS: 384.1 [M+H]⁺. ¹H NMR (400 MHz, CD₃OD) δ 7.65 – 7.50 (m, 1H), 7.46 – 7.31 (m, 2H), 7.20 – 6.97 (m, 1H), 5.51 – 5.31 (m, 1H), 4.52 – 4.25 (m, 2H), 3.92 – 3.75 (m, 1H), 3.37 (s, 2H), 1.37 (d, *J* = 6.8 Hz, 3H).

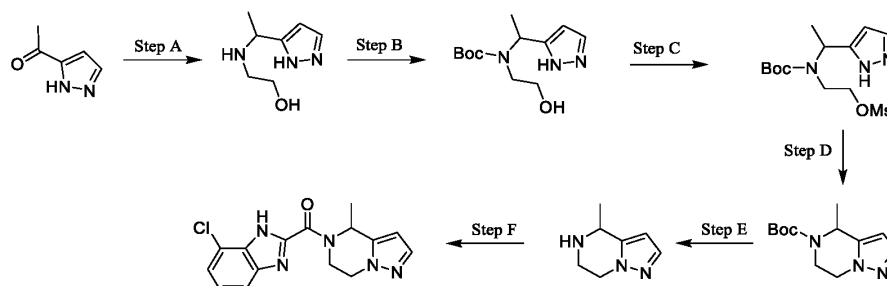
Examples 26A and 26B: (R) or (S)-(7-Chloro-1H-benzo[d]imidazol-2-yl)(6-methyl-3-(trifluoromethyl)-5,6-dihydroimidazo[1,5-a]pyrazin-7(8H)-yl)methanone and (R) or (S)-(7-

Chloro-1H-benzo[d]imidazol-2-yl)(6-methyl-3-(trifluoromethyl)-5,6-dihydroimidazo[1,5-a]pyrazin-7(8H)-yl)methanone



[00241] (7-Chloro-1H-benzo[d]imidazol-2-yl)(6-methyl-3-(trifluoromethyl)-5,6-dihydroimidazo[1,5-a]pyrazin-7(8H)-yl)methanone (7.90 g, 20.6 mmol) was separated by SFC separation (DAICEL CHIRALCEL OD (250 × 30 mm, 10 μm); flow rate: 30 mL/min; gradient: 38% B over 14 min; mobile phase A: heptane, mobile phase B: CO₂ - MeOH (0.1% NH₃H₂O) to afford a first eluted compound and a second eluted compound. First eluted compound (**Example 26A**): LC-MS: 384.1 [M+H]⁺. ¹H NMR (400 MHz, CDCl₃) δ 7.64 (br s, 1H), 7.45 – 7.38 (m, 1H), 7.37 – 7.29 (m, 1H), 7.11 (br d, *J* = 5.8 Hz, 1H), 7.07 – 6.72 (m, 1H), 5.53 – 4.59 (m, 2H), 4.47 – 4.21 (m, 2H), 1.43 – 1.37 (m, 3H). Second eluted compound (**Example 26B**): LC-MS: 384.1 [M+H]⁺. ¹H NMR (400 MHz, CDCl₃) δ 7.74 – 7.60 (m, 1H), 7.48 – 7.39 (m, 1H), 7.38 – 7.31 (m, 1H), 7.12 (br d, *J* = 5.1 Hz, 1H), 7.09 – 6.71 (m, 1H), 5.57 – 4.60 (m, 2H), 4.53 – 4.17 (m, 2H), 1.48 – 1.37 (m, 3H). The absolute stereochemistry for the first and second eluted compounds was not determined.

Example 27: (7-Chloro-1H-benzo[d]imidazol-2-yl)(4-methyl-6,7-dihydropyrazolo[1,5-a]pyrazin-5(4H)-yl)methanone



[00242] Step A: To a solution of 1-(1H-pyrazol-5-yl)ethan-1-one (500 mg, 4.54 mmol), 2-aminoethan-1-ol (277 mg, 4.54 mmol) in MeOH (8.00 mL) was added NaBH₃CN (571 mg, 9.08 mmol). The mixture was stirred at 20 °C for 1 h. The mixture was poured into H₂O (8.00 mL) and extracted with EtOAc (5.00 mL × 3). The combined organic layers were dried over Na₂SO₄ and concentrated under vacuum to give 2-((1-(1H-pyrazol-5-yl)ethyl)amino)ethan-1-ol. LC-MS: 156.2 [M+H]⁺.

[00243] Step B: To a solution of 2-((1-(1H-pyrazol-5-yl)ethyl)amino)ethan-1-ol (500 mg, 3.22 mmol) in MeOH (10.0 mL) and H₂O (3.00 mL) was added (Boc)₂O (703 mg, 3.22 mmol) and

K₂CO₃ (891 mg, 6.44 mmol). The mixture was stirred at 20 °C for 12 h. The mixture was poured into H₂O (15.0 mL) and extracted with EtOAc (6.00 mL x 3). The combined filtrates were concentrated under vacuum to give a residue which was purified by flash silica gel chromatography using a gradient of Petroleum ether/(Ethanol/Ethyl acetate = 3/1 ether from 1/100 to 1/2 to afford *tert*-butyl (1-(1*H*-pyrazol-5-yl)ethyl)(2-hydroxyethyl)carbamate. LC-MS: 256.2 [M+H]⁺.

[00244] Step C: To a solution of *tert*-butyl (1-(1*H*-pyrazol-5-yl)ethyl)(2-hydroxyethyl)carbamate (100 mg, 0.392 mmol) in DCM (1.00 mL) was added TEA (59.5 mg, 0.587 mmol), followed by MsCl (89.7 mg, 0.784 mmol) at 0 °C under nitrogen. The mixture was stirred at 20 °C for 12 h. The mixture was poured into saturated NaHCO₃ aqueous (1.00 mL) and extracted with DCM (1.00 mL x 3). The combined organic layers were dried over Na₂SO₄, filtered, and concentrated under vacuum to give a residue which was purified via preparative TLC (Petroleum ether / Ethyl acetate = 1/1, R_f = 0.4) to afford 2-((1-(1*H*-pyrazol-5-yl)ethyl)(*tert*-butoxycarbonyl)amino)ethyl methanesulfonate. LC-MS: 234.1 [M+H]⁺.

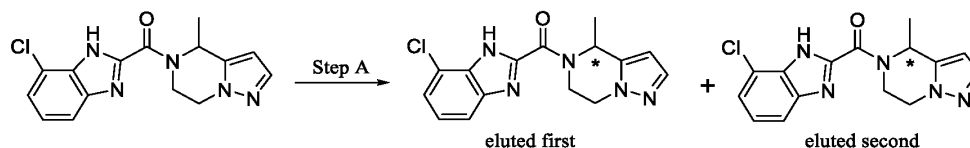
[00245] Step D: To a solution of 2-((1-(1*H*-pyrazol-5-yl)ethyl)(*tert*-butoxycarbonyl)amino)ethyl methanesulfonate (25.0 mg, 0.075 mmol) in DMF (1.50 mL) was added NaH (9.00 mg, 0.224 mmol, 60% purity). The mixture was stirred at 20 °C for 12 h. The mixture was poured into H₂O (2.00 mL) and extracted with EtOAc (1.00 mL x 3). The combined filtrates layers were dried over Na₂SO₄ and concentrated under vacuum to give *tert*-butyl 4-methyl-6,7-dihydropyrazolo[1,5-*a*]pyrazine-5(4*H*)-carboxylate. LC-MS: 238.2 [M+H]⁺.

[00246] Step E: To a solution of *tert*-butyl 4-methyl-6,7-dihydropyrazolo[1,5-*a*]pyrazine-5(4*H*)-carboxylate (12.0 mg, 0.050 mmol) in EtOAc (0.50 mL) was added HCl/EtOAc (4M, 0.50 mL). The mixture was stirred at 20 °C for 1 h. The mixture was concentrated under reduced pressure to give the 4-methyl-4,5,6,7-tetrahydropyrazolo[1,5-*a*]pyrazine.

[00247] Step F: To a solution of 4-methyl-4,5,6,7-tetrahydropyrazolo[1,5-*a*]pyrazine (11.0 mg, 0.080 mmol, HCl salt) and 7-chloro-1*H*-benzo[*d*]imidazole-2-carboxylic acid (15.8 mg, 0.080 mmol) in DMF (1.00 mL) was added HATU (30.5 mg, 0.080 mmol) and DIEA (20.7 mg, 0.160 mmol). The mixture was stirred at 20 °C for 3 h. The mixture was poured into H₂O (1.00 mL) and extracted with EtOAc (1.00 mL x 2). The combined organic layers were dried over Na₂SO₄, filtered and concentrated under vacuum to give a residue which was purified by preparative HPLC (column: Phenomenex Luna C18 (75 × 30 mm, 3 μm); flow rate: 25 mL/min; gradient: 25% – 55% B over 8 min; mobile phase A: 0.04% aqueous HCl mobile phase B: acetonitrile) to afford (7-chloro-1*H*-benzo[*d*]imidazol-2-yl)(4-methyl-6,7-dihydropyrazolo[1,5-*a*]pyrazin-5(4*H*)-yl)methanone. LC-MS: 315.9 [M+H]⁺. ¹H NMR (400 MHz, DMSO-*d*₆) δ 7.61 – 7.52 (m, 1H),

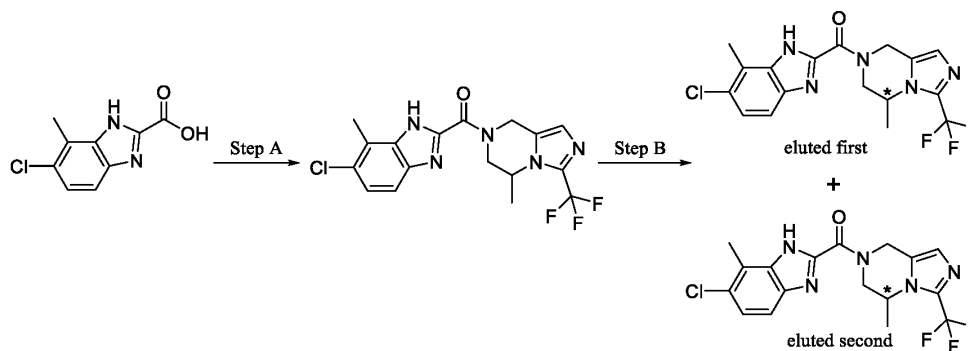
7.51 – 7.42 (m, 1H), 7.38 (s, 1H), 7.36 – 7.29 (m, 1H), 6.78 – 6.55 (m, 1H), 6.29 – 6.19 (m, 1H), 6.02 – 5.88 (m, 1H), 5.87 – 5.77 (m, 1H), 4.89 – 4.31 (m, 1H), 4.27 – 4.04 (m, 1H), 3.96 – 3.51 (m, 1H), 1.75 – 1.46 (m, 3H).

Examples 27A and 27B: (R) or (S)-(7-Chloro-1H-benzo[d]imidazol-2-yl)(4-methyl-6,7-dihydropyrazolo[1,5-a]pyrazin-5(4H)-yl)methanone and (R) or (S)-(7-Chloro-1H-benzo[d]imidazol-2-yl)(4-methyl-6,7-dihydropyrazolo[1,5-a]pyrazin-5(4H)-yl)methanone



[00248] ((7-Chloro-1H-benzo[d]imidazol-2-yl)(4-methyl-6,7-dihydropyrazolo[1,5-a]pyrazin-5(4H)-yl)methanone (12 mg, 0.035 mmol) was further separation by SFC separation((DAICEL CHIRALCEL OZ (250 × 30 mm, 10 μm); flow rate: 64 mL/min; gradient: 30% B over 4 min; mobile phase A: CO₂, mobile phase B: IPA(0.1%NH₃H₂O)) to afford a first eluted compound and a second eluted compound. First eluted compound (**Example 27A**): LC-MS: 316.1 [M+H]⁺. ¹H NMR (400 MHz, DMSO-*d*₆) δ 13.59 (br s, 1H), 7.66 – 7.49 (m, 1H), 7.48 – 7.42 (m, 1H), 7.40 – 7.36 (m, 1H), 7.35 – 7.28 (m, 2H), 6.78 – 6.16 (m, 1H), 6.06 – 5.77 (m, 1H), 4.91 – 4.29 (m, 1H), 4.25 – 4.02 (m, 1H), 3.95 – 3.52 (m, 1H), 1.75 – 1.46 (m, 3H). Second eluted compound (**Example 27B**): LC-MS: 316.1 [M+H]⁺. ¹H NMR (400 MHz, DMSO-*d*₆) δ 13.68 – 13.49 (m, 1H), 7.56 – 7.48 (m, 1H), 7.44 (br s, 1H), 7.41 – 7.36 (m, 1H), 7.33 – 7.30 (m, 2H), 6.82 – 6.16 (m, 1H), 6.11 – 5.73 (m, 1H), 4.94 – 4.29 (m, 1H), 4.26 – 4.00 (m, 1H), 3.94 – 3.50 (m, 1H), 1.77 – 1.44 (m, 3H). The absolute stereochemistry for the first and second eluted compounds was not determined.

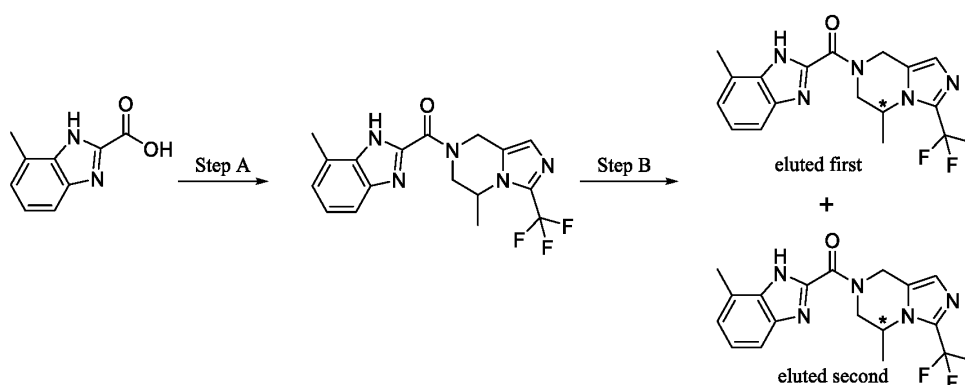
Examples 28A and 28B: (R) or (S)-(6-Chloro-7-methyl-1H-benzo[d]imidazol-2-yl)(5-methyl-3-(trifluoromethyl)-5,6-dihydroimidazo[1,5-a]pyrazin-7(8H)-yl)methanone and (R) or (S)-(6-Chloro-7-methyl-1H-benzo[d]imidazol-2-yl)(5-methyl-3-(trifluoromethyl)-5,6-dihydroimidazo[1,5-a]pyrazin-7(8H)-yl)methanone



[00249] Step A: Racemic (6-chloro-7-methyl-1H-benzo[d]imidazol-2-yl)(5-methyl-3-(trifluoromethyl)-5,6-dihydroimidazo[1,5-a]pyrazin-7(8H)-yl)methanone was prepared from 5-methyl-3-(trifluoromethyl)-5,6,7,8-tetrahydroimidazo[1,5-a]pyrazine and 6-chloro-7-methyl-1H-benzo[d]imidazole-2-carboxylic acid according to the procedure of Example 1, Step A. LC-MS: 398.1 [M+H]⁺.

[00250] Step B: Racemic (6-chloro-7-methyl-1H-benzo[d]imidazol-2-yl)(5-methyl-3-(trifluoromethyl)-5,6-dihydroimidazo[1,5-a]pyrazin-7(8H)-yl)methanone (20.0 mg, HCl salt) was purified by SFC separation ((DAICEL CHIRALPAK AD (250 × 30 mm, 10 μm); flow rate: 64 mL/min; gradient: 38% B over 15 min; mobile phase A: CO₂, mobile phase B: EtOH (0.1% NH₃H₂O)) to afford a first eluted compound and a second eluted compound. First eluted compound (**Example 28A**): LC-MS: 398.1 [M+H]⁺. ¹H NMR (400 MHz, CDCl₃) δ 10.54 – 10.04 (m, 1H), 7.70 (d, J = 3.8 Hz, 1H), 7.59 (d, J = 8.6 Hz, 1H), 7.11 – 6.62 (m, 2H), 5.63 – 5.05 (m, 1H), 4.58 (br d, J = 17.5 Hz, 2H), 3.89 – 3.44 (m, 1H), 2.75 (s, 3H), 1.67 – 1.51 (m, 3H). Second eluted compound (**Example 28B**): LC-MS: 398.1 [M+H]⁺. ¹H NMR (400 MHz, CDCl₃) δ 10.42 – 10.08 (m, 1H), 7.70 – 7.30 (m, 2H), 7.10 – 6.65 (m, 2H), 5.64 – 5.06 (m, 1H), 4.96 – 4.52 (m, 2H), 3.89 – 3.42 (m, 1H), 2.80 – 2.53 (m, 3H), 1.64 – 1.51 (m, 3H). The absolute stereochemistry for the first and second eluted compounds was not determined.

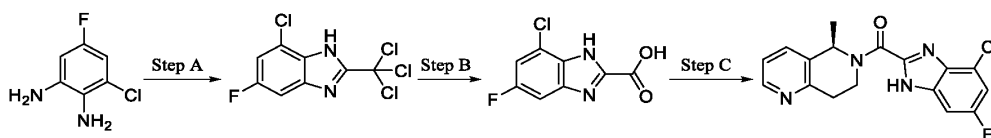
Examples 29A and 29B: (R) or (S)-(7-Methyl-1H-benzo[d]imidazol-2-yl)(5-methyl-3-(trifluoromethyl)-5,6-dihydroimidazo[1,5-a]pyrazin-7(8H)-yl)methanone and (R) or (S)-(7-Methyl-1H-benzo[d]imidazol-2-yl)(5-methyl-3-(trifluoromethyl)-5,6-dihydroimidazo[1,5-a]pyrazin-7(8H)-yl)methanone



[00251] Step A: Racemic (7-methyl-1H-benzo[d]imidazol-2-yl)(5-methyl-3-(trifluoromethyl)-5,6-dihydroimidazo[1,5-a]pyrazin-7(8H)-yl)methanone was prepared from 5-methyl-3-(trifluoromethyl)-5,6,7,8-tetrahydroimidazo[1,5-a]pyrazine and 7-methyl-1H-benzo[d]imidazole-2-carboxylic acid according to the procedure of Example 1, Step A. LC-MS: 364.1 [M+H]⁺.

[00252] Step B: Racemic (7-methyl-1H-benzo[d]imidazol-2-yl)(5-methyl-3-(trifluoromethyl)-5,6-dihydroimidazo[1,5-a]pyrazin-7(8H)-yl)methanone (10.0 mg, 0.0275 mmol, HCl salt) was further separated by SFC separation ((DAICEL CHIRALCEL OZ (250 × 25 mm, 10 μm); flow rate: 64 mL/min; gradient: 35% B over 4 min; mobile phase A: CO₂, mobile phase B: MeOH(0.1%NH₃H₂O)) to afford a first eluted compound and a second eluted compound. First eluted compound (**Example 29A**): LC-MS: 364.1 [M+H]⁺. ¹H NMR (400 MHz, CDCl₃) δ 10.37 – 10.12 (m, 1H), 7.77 – 7.28 (m, 2H), 7.23 – 6.74 (m, 3H), 5.71 – 5.05 (m, 1H), 4.98 – 4.47 (m, 2H), 3.89 – 3.43 (m, 1H), 2.80 – 2.50 (m, 3H), 1.62 – 1.56 (m, 3H). Second eluted compound (**Example 29B**): LC-MS: 364.1[M+H]⁺. ¹H NMR (400 MHz, CDCl₃) δ 10.45 – 10.12 (m, 1H), 7.76 – 7.20 (m, 2H), 7.16 – 6.61 (m, 3H), 5.68 – 4.95 (m, 1H), 4.93 – 4.43 (m, 2H), 3.81 – 3.28 (m, 1H), 2.71 – 2.40 (m, 3H), 1.49 (br s, 3H). The absolute stereochemistry for the first and second eluted compounds was not determined.

Example 30: (R)-(4-Chloro-6-fluoro-1H-benzo[d]imidazol-2-yl)(5-methyl-7,8-dihydro-1,6-naphthyridin-6(5H)-yl)methanone



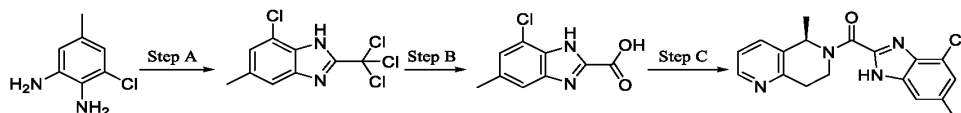
[00253] Step A: A mixture of 3-chloro-5-fluorobenzene-1,2-diamine (200 mg, 1.26 mmol) and methyl 2,2,2-trichloroethanimidate (219 mg, 1.25 mmol) in AcOH (2.00 mL) was stirred at 20 °C for 2 h. The reaction mixture was filtered and the filter cake was washed with 10.0 mL water, dried in vacuum to give 7-chloro-5-fluoro-2-(trichloromethyl)-1H-benzo[d]imidazole. LC-MS: 288.9 [M+H]⁺.

[00254] Step B: A mixture of 7-chloro-5-fluoro-2-(trichloromethyl)-1H-benzo[d]imidazole (360 mg, 1.25 mmol) in NaOH (2M in aqueous, 4.00 mL) was stirred at 20 °C for 2 h. The reaction mixture was poured into H₂O (5.0 mL) and extracted with MTBE (5.00 mL x 2). The aqueous phase was adjusted to pH 4 by adding HCl (1M aqueous) and extracted with DCM (5.00 mL x 3). The combined organic layers were dried over Na₂SO₄, filtered, and concentrated under vacuum to give 7-chloro-5-fluoro-1H-benzo[d]imidazole-2-carboxylic acid. LC-MS: 213.1 [M+H]⁺.

[00255] Step C: A mixture of 7-chloro-5-fluoro-1H-benzo[d]imidazole-2-carboxylic acid (30.0 mg, 0.140 mmol), (R)-5-methyl-5,6,7,8-tetrahydro-1,6-naphthyridine (21.0 mg, 0.112 mmol), HATU (27.0 mg, 0.070 mmol) and DIEA (54.0 mg, 0.419 mmol) in DMF (2.00 mL) was stirred at 20 °C for 1 h. The mixture was concentrated under vacuum at 30 °C to give a residue which was purified by preparative HPLC (Phenomenex Luna C18 column 75 × 30mm × 3μm); flow rate:

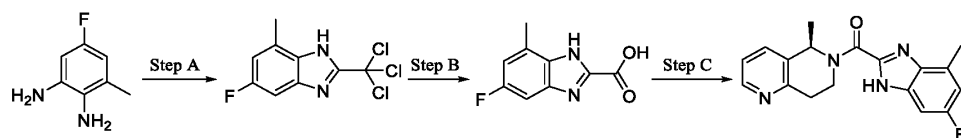
25 mL/min; gradient: 15% – 40% B over 8 min; mobile phase A: 0.04% aqueous HCl, mobile phase B: acetonitrile) to afford (R)-(4-chloro-6-fluoro-1H-benzo[d]imidazol-2-yl)(5-methyl-7,8-dihydro-1,6-naphthyridin-6(5H)-yl)methanone. LC-MS: 344.9 [M+H]⁺. ¹H NMR (400 MHz, MeOD) δ 8.77 – 8.48 (m, 2H), 8.01 – 7.86 (m, 1H), 7.36 – 6.97 (m, 2H), 6.09 – 5.88 (m, 1H), 4.97 (br dd, *J* = 4.6, 13.2 Hz, 1H), 3.84 – 3.31 (m, 3H), 1.96 – 1.64 (m, 3H).

Example 31: (R)-(4-Chloro-6-methyl-1H-benzo[d]imidazol-2-yl)(5-methyl-7,8-dihydro-1,6-naphthyridin-6(5H)-yl)methanone



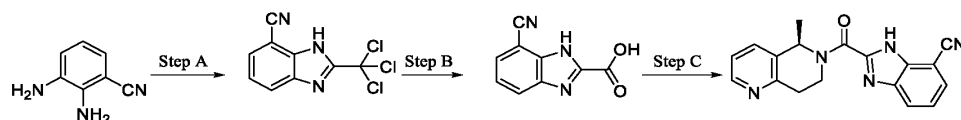
[00256] (R)-(4-Chloro-6-methyl-1H-benzo[d]imidazol-2-yl)(5-methyl-7,8-dihydro-1,6-naphthyridin-6(5H)-yl)methanone was prepared from 3-chloro-5-methylbenzene-1,2-diamine according to the procedure of Example 30, Steps A, B, and C. LC-MS: 341.1 [M+H]⁺. ¹H NMR (400 MHz, DMSO-*d*₆) δ 8.83 – 8.70 (m, 1H), 8.67 – 8.47 (m, 1H), 8.00 – 7.83 (m, 1H), 7.43 – 7.17 (m, 2H), 6.84 – 5.87 (m, 1H), 5.86 – 4.58 (m, 1H), 3.53 – 3.22 (m, 3H), 2.43 (s, 3H), 1.83 – 1.56 (m, 3H).

Example 32: (R)-(6-Fluoro-4-methyl-1H-benzo[d]imidazol-2-yl)(5-methyl-7,8-dihydro-1,6-naphthyridin-6(5H)-yl)methanone



[00257] (R)-(6-Fluoro-4-methyl-1H-benzo[d]imidazol-2-yl)(5-methyl-7,8-dihydro-1,6-naphthyridin-6(5H)-yl)methanone was prepared from 5-fluoro-3-methylbenzene-1,2-diamine according to the procedure of Example 30, Steps A, B, and C. LC-MS: 344.9 [M+H]⁺. ¹H NMR (400 MHz, MeOD) δ 8.77 – 8.48 (m, 2H), 8.01 – 7.86 (m, 1H), 7.36 – 6.97 (m, 2H), 6.09 – 5.88 (m, 1H), 4.97 (br dd, *J* = 4.6, 13.2 Hz, 1H), 3.84 – 3.31 (m, 3H), 1.96 – 1.64 (m, 3H).

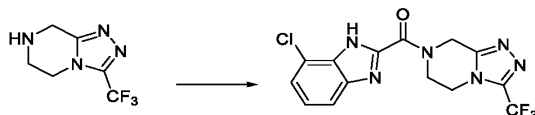
Example 33: (R)-2-(5-Methyl-5,6,7,8-tetrahydro-1,6-naphthyridine-6-carbonyl)-1H-benzo[d]imidazole-7-carbonitrile



[00258] (R)-2-(5-Methyl-5,6,7,8-tetrahydro-1,6-naphthyridine-6-carbonyl)-1H-benzo[d]imidazole-7-carbonitrile was prepared from 2,3-diaminobenzonitrile according to the procedure of Example 30, Steps A, B, and C. LC-MS: 318.0 [M+H]⁺. ¹H NMR (400 MHz,

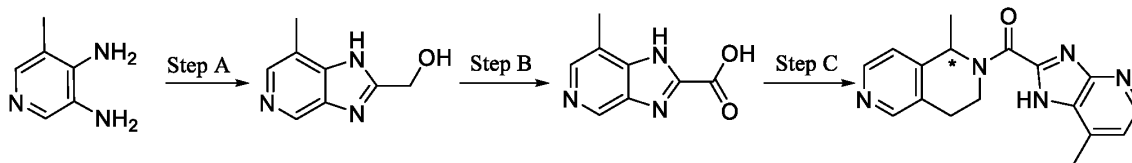
CDCl_3) δ 11.85 – 11.12 (m, 1H), 8.52 – 8.10 (m, 1H), 7.83 – 7.69 (m, 2H), 7.64 – 7.38 (m, 2H), 7.21 (br dd, $J=4.9, 7.4$ Hz, 1H), 6.54 – 4.92 (m, 2H), 3.90 – 3.43 (m, 1H), 3.42 – 3.09 (m, 2H), 1.86 – 1.65 (m, 3H).

Example 34: (7-Chloro-1H-benzo[d]imidazol-2-yl)(3-(trifluoromethyl)-5,6-dihydro-[1,2,4]triazolo[4,3-a]pyrazin-7(8H)-yl)methanone



[00259] The title compound was prepared from 3-(trifluoromethyl)-5,6,7,8-tetrahydro-[1,2,4]triazolo[4,3-a]pyrazine and 7-chloro-1H-benzimidazole-2-carboxylic acid according to the procedure of Example 1, Step A. LC-MS: 370.9 $[\text{M}+\text{H}]^+$. ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ 13.68 – 13.55 (m, 1H), 7.60 – 7.25 (m, 3H), 6.17 – 5.10 (m, 2H), 5.07 – 4.37 (m, 2H), 4.31 – 4.15 (m, 2H).

Example 35: (7-Methyl-1H-imidazo[4,5-b]pyridin-2-yl)(5-methyl-7,8-dihydro-1,6-naphthyridin-6(5H)-yl)methanone



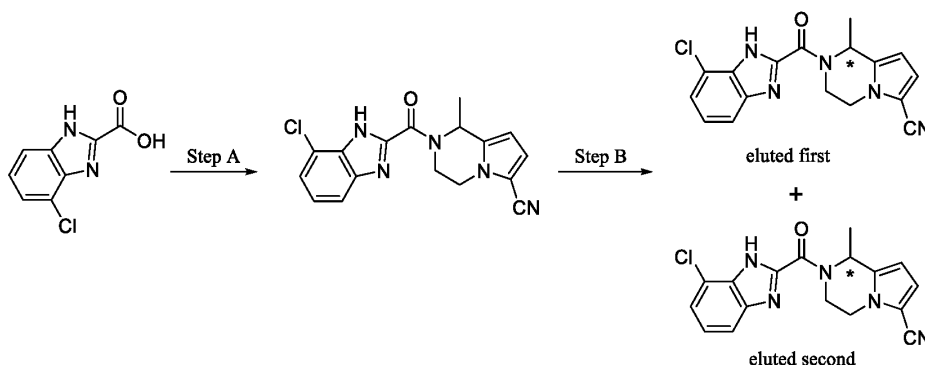
[00260] Step A: A solution of 4-methylpyridine-2,3-diamine (200 mg, 1.62 mmol) in 2-hydroxyacetic acid (266 mg, 3.51 mmol) was stirred at 140 °C for 3 h. The reaction mixture was allowed to cool to room temperature and treated with saturated NaHCO_3 aqueous (5.0 mL). The resulting precipitates are filtered and the cake was dried in vacuum to give 7-methyl-2-(trichloromethyl)-1H-imidazo[4,5-b]pyridine. LC-MS: 162.1 $[\text{M}+\text{H}]^+$.

[00261] Step B: A solution of KMnO_4 (261 mg, 1.65 mmol) in H_2O (18.0 mL) was stirred at 100 °C. Then (7-methyl-1H-imidazo[4,5-b]pyridin-2-yl)methanol (180 mg, 1.10 mmol) and Na_2CO_3 (85.3 mg, 0.805 mmol) in H_2O (18.0 mL) was added. The mixture was stirred at 100 °C for 2 h. The mixture was filtered and the filtrate was allowed to cool to room temperature, acidified to pH 2-3 with HCl (12M). The resulting precipitate was filtered and the cake was dried in vacuum to give 7-methyl-1H-imidazo[4,5-b]pyridine-2-carboxylic acid. LC-MS: 176.1 $[\text{M}+\text{H}]^+$.

[00262] Step C: To a solution of 5-methyl-5,6,7,8-tetrahydro-1,6-naphthyridine (10.4 mg, 0.056 mmol) in DMF (0.50 mL) was added 7-methyl-1H-imidazo[4,5-b]pyridine-2-carboxylic acid (10.0 mg, 0.056 mmol), DIEA (21.9 mg, 0.169 mmol) and HATU (10.7 mg, 0.028 mmol).

The mixture was stirred at 25 °C for 1 h. The reaction mixture was poured into H₂O (5.00 mL) and extracted with EtOAc (5.00 mL x 3). The combined organic layers were dried over Na₂SO₄, filtered, and concentrated under vacuum to give a residue which was purified by preparative HPLC (Phenomenex Gemini C18 column (150×40 mm, 10 μm); flow rate: 60 mL/min; gradient: 43% – 73% B over 8 min; mobile phase A: 10 mM aqueous NH₄HCO₃, mobile phase B: acetonitrile) to afford (7-methyl-1H-imidazo[4,5-b]pyridin-2-yl)(5-methyl-7,8-dihydro-1,6-naphthyridin-6(5H)-yl)methanone. LC-MS: 308.0 [M+H]⁺. ¹H NMR (400 MHz, DMSO-*d*₆) δ 13.61 (br d, *J* = 7.1 Hz, 1H), 8.48 – 8.25 (m, 2H), 7.85 – 7.61 (m, 1H), 7.35 – 7.06 (m, 2H), 6.47 – 5.64 (m, 1H), 5.51 – 4.68 (m, 1H), 3.75 – 3.38 (m, 1H), 3.23 – 2.90 (m, 2H), 2.60 (br s, 3H), 1.81 – 1.49 (m, 3H).

Examples 36A and 36B: (R) or (S)-2-(7-Chloro-1H-benzo[d]imidazole-2-carbonyl)-1-methyl-1,2,3,4-tetrahydropyrrolo[1,2-a]pyrazine-6-carbonitrile and (R) or (S)-2-(7-Chloro-1H-benzo[d]imidazole-2-carbonyl)-1-methyl-1,2,3,4-tetrahydropyrrolo[1,2-a]pyrazine-6-carbonitrile

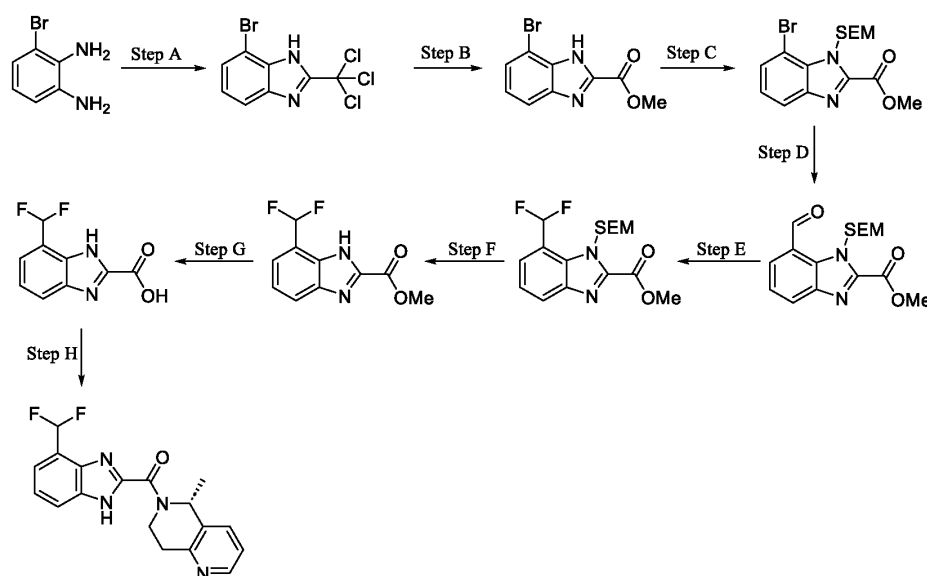


[00263] Step A: Racemic 2-(7-chloro-1H-benzo[d]imidazole-2-carbonyl)-1-methyl-1,2,3,4-tetrahydropyrrolo[1,2-a]pyrazine-6-carbonitrile was prepared from 1-methyl-1,2,3,4-tetrahydropyrrolo[1,2-a]pyrazine-6-carbonitrile and 4-chloro-1H-benzo[d]imidazole-2-carboxylic acid according to the procedure of Example 1, Step A. LC-MS: 339.9 [M+H]⁺.

[00264] Step B: Racemic 2-(7-Chloro-1H-benzo[d]imidazole-2-carbonyl)-1-methyl-1,2,3,4-tetrahydropyrrolo[1,2-a]pyrazine-6-carbonitrile (40.0 mg, 0.120 mmol) was separated by SFC separation (Phenomenex-CHIRALPAK IH (250 × 30 mm, 10 μm); flow rate: 30 mL/min; gradient: 60% B over 14 min; mobile phase A: heptane, mobile phase B: EtOH(0.1% NH₃H₂O) to afford a first eluted compound and a second eluted compound. First eluted compound (**Example 36A**): LC-MS: 339.9 [M+H]⁺. ¹H NMR (400 MHz, CDCl₃) δ 10.42 – 10.08 (m, 1H), 7.73 – 7.20 (m, 3H), 6.91 – 6.41 (m, 1H), 6.06 – 4.89 (m, 1H), 4.38 – 3.37 (m, 2H), 2.10 (s, 2H), 1.74 – 1.52 (m, 2H), 1.28 – 0.41 (m, 2H). Second eluted compound (**Example 36B**): LC-MS:

339.9 $[M+H]^+$. 1H NMR (400 MHz, $CDCl_3$) δ 10.53 – 10.23 (m, 1H), 7.72 – 7.19 (m, 3H), 6.79 – 6.50 (m, 1H), 6.06 – 4.91 (m, 1H), 4.37 – 3.36 (m, 2H), 2.10 (s, 2H), 1.75 – 1.51 (m, 2H), 1.28 – 0.48 (m, 2H). The absolute stereochemistry for the first and second eluted compounds was not determined.

Example 37: (*R*)-(4-(Difluoromethyl)-1H-benzo[d]imidazol-2-yl)(5-methyl-7,8-dihydro-1,6-naphthyridin-6(5H)-yl)methanone



[00265] Step A: A solution of 3-bromobenzene-1,2-diamine (2 g, 10.7 mmol) and methyl 2,2,2-trichloroethanimidate (1.89 g, 10.7 mmol) in AcOH (20.0 mL) was stirred at 20 °C for 1 hr. The mixture was concentrated to give 7-bromo-2-(trichloromethyl)-1H-benzimidazole. LC-MS: 312.9 $[M+H]^+$.

[00266] Step B: A solution of Na_2CO_3 (809 mg, 7.63 mmol) in H_2O (8.00 mL) was added to a solution of 7-bromo-2-(trichloromethyl)-1H-benzimidazole (2.40 g, 7.63 mmol) in MeOH (100 mL). The solution was stirred at 100 °C for 24 h. The reaction mixture was allowed to cool to room temperature and half of the solvent was removed in vacuum. The solution was then added to well-stirred water (5.00 mL) over 10 min. The solution was extracted with EtOAc (5.00 mL x 3). The combined organic phases were washed with brine (2.00 mL), dried over Na_2SO_4 , filtered, and concentrated under vacuum to give a residue which was purified by flash silica gel chromatography using a gradient of EtOAc/petroleum ether from 0/1 to 1/1 to afford methyl 7-bromo-1H-benzimidazole-2-carboxylate. LC-MS: 256.9 $[M+H]^+$.

[00267] Step C: To a solution of methyl 7-bromo-1H-benzimidazole-2-carboxylate (500 mg, 1.96 mmol) in DMF (8.00 mL) was added NaH (157 mg, 3.92 mmol, 60% purity). The mixture was stirred at 0 °C for 30 min, then SEM-Cl (392 mg, 2.35 mmol) was added. The mixture was

stirred at 20 °C for 12 h. The reaction mixture was poured into H₂O (5.00ml), then extracted with EtOAc (3.00 mL x 3). The combined organic layers were dried over Na₂SO₄, filtered and concentrated under reduced pressure to give a residue which was purified by flash silica gel chromatography using a gradient of EtOAc/petroleum ether from 0/1 to 1/10 to afford methyl 7-bromo-1-(2-trimethylsilylethoxymethyl)benzimidazole-2-carboxylate. LC-MS: 385.2 [M+H]⁺.

[00268] Step D: A mixture of methyl 7-bromo-1-(2-trimethylsilylethoxymethyl)benzimidazole-2-carboxylate (70.0 mg, 0.182 mmol), Pd(dppf)Cl₂ (33.2 mg, 0.045 mmol), TES (83.3 mg, 0.363 mmol) and Na₂CO₃ (19.3 mg, 0.182 mmol) in DMF (2.00 mL) was degassed and purged with CO for 3 times, and then the mixture was stirred at 70 °C for 24 h under CO (50 Psi) atmosphere. The reaction mixture was concentrated under reduced pressure to give a residue which was purified via preparative TLC (Petroleum ether / Ethyl acetate = 3/1, R_f = 0.3) to afford methyl 7-formyl-1-(2-trimethylsilylethoxymethyl)benzimidazole-2-carboxylate. LC-MS: 335.2 [M+H]⁺.

[00269] Step E: To a solution of methyl 7-formyl-1-(2-trimethylsilylethoxymethyl)benzimidazole-2-carboxylate (30.0 mg, 0.089 mmol) in DCM (1.00 mL) was added DAST (145 mg, 0.897 mmol) at 0 °C. The mixture was stirred at 20 °C for 12 h. The reaction mixture was poured into H₂O (2.00 mL) and extracted with DCM (2.00 mL x 3). The combined organic layers were dried over Na₂SO₄, filtered and concentrated under reduced pressure to give a residue which was purified via preparative TLC (Petroleum ether / Ethyl acetate = 3/1, R_f = 0.7) to afford methyl 7-(difluoromethyl)-1-(2-trimethylsilylethoxymethyl)benzimidazole-2-carboxylate. LC-MS: 357.2 [M+H]⁺.

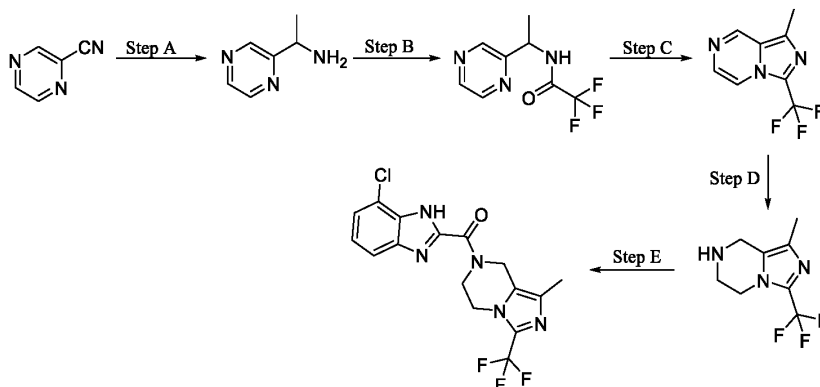
[00270] Step F: A solution of methyl 7-(difluoromethyl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-benzo[*d*]imidazole-2-carboxylate (15.0 mg, 0.042 mmol) in EtOH (0.600 mL) and HCl (0.200 mL) was stirred at 80 °C for 0.5 h. The reaction mixture was allowed to cool to room temperature, poured into saturated NaHCO₃ aqueous (1.00 mL) and extracted with DCM (1.00 mL x 3). The combined organic layers were dried over Na₂SO₄, filtered, and concentrated under vacuum to give methyl 7-(difluoromethyl)-1*H*-benzo[*d*]imidazole-2-carboxylate. LC-MS: 227.1 [M+H]⁺.

[00271] Step G: To a solution of methyl 7-(difluoromethyl)-1*H*-benzo[*d*]imidazole-2-carboxylate (10.0 mg, 0.044 mmol) in THF (0.050 mL) and EtOH (0.050 mL) was added NaOH aqueous (2M, 0.221 mL). The mixture was stirred at 20 °C for 2 h. The mixture was concentrated under vacuum at 20 °C to give 7-(difluoromethyl)-1*H*-benzo[*d*]imidazole-2-carboxylic acid. LC-MS: 213.0 [M+H]⁺.

[00272] Step H: To a solution of 7-(difluoromethyl)-1*H*-benzo[*d*]imidazole-2-carboxylic acid (8.00 mg, 0.037 mmol, HCl salt) and (*R*)-5-methyl-5,6,7,8-tetrahydro-1,6-naphthyridine (13.1

mg, 0.070 mmol) in DMF (0.500 mL) was added DIEA (18.3 mg, 0.141 mmol) and HATU (13.4 mg, 0.035 mmol). The mixture was stirred at 20 °C for 1 h. The reaction mixture was poured into water (2.00 mL) and extracted with EtOAc (1.00 mL x 2). The combined organic layers were dried over Na₂SO₄, filtered, and concentrated under vacuum to give a residue which was purified by preparative HPLC (Phenomenex luna C18 column (80 × 30 mm, 3 μm); flow rate: 30 mL/min; gradient: 1% – 30% B over 8 min; mobile phase A: 0.04% aqueous HCl, mobile phase B: acetonitrile) to afford (*R*)-(4-(difluoromethyl)-1*H*-benzo[*d*]imidazol-2-yl)(5-methyl-7,8-dihydro-1,6-naphthyridin-6(5*H*)-yl)methanone. LC-MS: 343.1 [M+H]⁺. ¹H NMR (400 MHz, DMSO-*d*₆) δ 8.76 – 8.67 (m, 1H), 8.50 – 8.29 (m, 1H), 7.90 – 7.72 (m, 2H), 7.60 – 7.34 (m, 3H), 5.94 – 5.66 (m, 1H), 3.73 (br s, 1H), 3.45 – 3.38 (m, 1H), 3.26 – 3.25 (m, 1H), 3.23 – 3.16 (m, 2H), 1.83 – 1.73 (m, 1H), 1.76 (d, *J* = 6.8 Hz, 2H).

Example 38: (7-Chloro-1*H*-benzo[*d*]imidazol-2-yl)(1-methyl-3-(trifluoromethyl)-5,6-dihydroimidazo[1,5-*a*]pyrazin-7(8*H*)-yl)methanone



[00273] Step A: A solution of MeMgBr (3M, 10.9 mL) was added into a solution of pyrazine-2-carbonitrile (3.00 g, 28.5 mmol) in THF (30.0 mL) at 0 °C. The mixture was warmed to 25 °C slowly, further stirred for 0.5 h, and followed by adding MeOH (60.0 mL) and NaBH₄ (2.16 g, 57.1 mmol) in portions. The mixture was stirred at 25 °C for 10 h. The mixture was poured into water (100 mL) and NaOH (2M aqueous, 100 mL), extracted with EtOAc (100 mL x 3). The combined organic layers were washed in turn with water (80.0 mL x 3) and brine (80.0 mL), dried over Na₂SO₄, filtered, and concentrated under vacuum to give 1-(pyrazin-2-yl)ethan-1-amine. LC-MS: 124.0 [M+H]⁺.

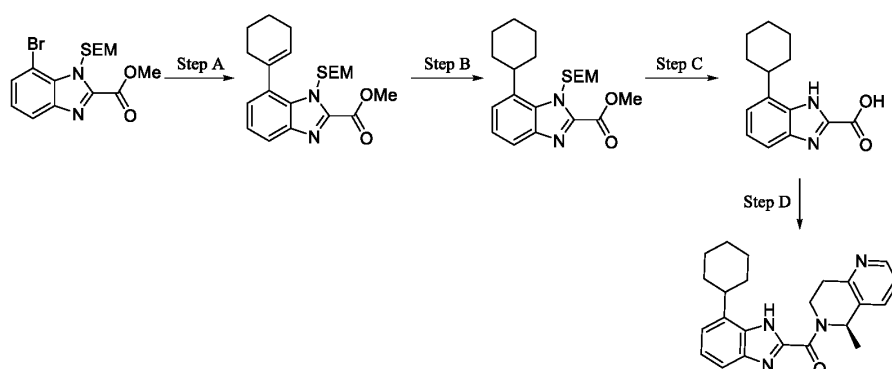
[00274] Step B: To a solution of 1-(pyrazin-2-yl)ethan-1-amine (1.27 g, 10.3 mmol) in DCM (10.0 mL) was added TFAA (4.33 g, 20.6 mmol). The mixture was stirred at 20 °C for 3 h. The mixture was concentrated under vacuum to give 2,2,2-trifluoro-N-(1-(pyrazin-2-yl)ethyl)acetamide. LC-MS: 220.2 [M+H]⁺.

[00275] Step C: To a solution of 2,2,2-trifluoro-N-(1-(pyrazin-2-yl)ethyl)acetamide (750 mg, 3.42 mmol) in POCl₃ (10.0 mL) was added P₂O₅ (607 mg, 4.28 mmol). The resulting mixture was stirred at 100 °C for 12 h. The mixture was concentrated under vacuum to give a residue which was poured into ice-water (20.0 mL), basified with Na₂CO₃ (solid) to pH 8, and extracted with EtOAc (20.0 mL x 2). The combined organic phase was washed with water (10.0 mL x 2) and brine (10.0 mL), dried over Na₂SO₄, filtered, and concentrated under vacuum to give a residue which was purified by flash silica gel chromatography using a gradient of EtOAc/petroleum ether from 0/1 to 1/1 to afford 1-methyl-3-(trifluoromethyl)imidazo[1,5-a]pyrazine. LC-MS: 202.2 [M+H]⁺.

[00276] Step D: To a solution of 1-methyl-3-(trifluoromethyl)imidazo[1,5-a]pyrazine (300 mg, 1.49 mmol) in 2,2,2-trifluoroethanol (6.00 mL) was added palladium on carbon (10% purity, 317 mg) under a nitrogen atmosphere. The suspension was degassed and purged with hydrogen and repeated two times. The mixture was stirred at 20 °C for 3 h under a hydrogen atmosphere. The suspension was filtered through a pad of Celite and the pad was washed with 2,2,2-trifluoroethanol (6.00 mL x 3). The combined filtrates were concentrated under vacuum to give a residue which was purified by HPLC (Phenomenex Luna C18 (75 x 30 mm, 3 µm); flow rate: 25 mL/min; gradient: 1% – 5% B over 8 min; mobile phase A: 0.04% aqueous HCl, mobile phase B: acetonitrile) to afford 1-methyl-3-(trifluoromethyl)-5,6,7,8-tetrahydroimidazo[1,5-a]pyrazine. LC-MS: 206.1 [M+H]⁺.

[00277] Step E: A mixture of 1-methyl-3-(trifluoromethyl)-5,6,7,8-tetrahydroimidazo[1,5-a]pyrazine (100 mg, 0.487 mmol), 7-chloro-1H-benzimidazole-2-carboxylic acid (95.8 mg, 0.487 mmol), HATU (185 mg, 0.487 mmol) and DIEA (189 mg, 1.46 mmol) in DMF (3.00 mL) was stirred at 25 °C for 1 h. The mixture was poured into H₂O (3.00 mL) at 0 °C, and extracted with EtOAc (3.00 mL x 2). The combined organic phase was washed with brine (4.00 mL), dried over Na₂SO₄, filtered, and concentrated to give a residue which was purified by preparative HPLC (Phenomenex Luna C18 column (100 x 30 mm, 10 µm); flow rate: 25 mL/min; gradient: 30% – 60% B over 8 min; mobile phase A: 10 mM aqueous NH₄HCO₃, mobile phase B: acetonitrile) to afford (7-chloro-1H-benzo[d]imidazol-2-yl)(1-methyl-3-(trifluoromethyl)-5,6-dihydroimidazo[1,5-a]pyrazin-7(8H)-yl)methanone. LC-MS: 384.2 [M+H]⁺. ¹H NMR (400 MHz, CDCl₃) δ 10.61 – 10.30 (m, 1H), 7.85 – 7.29 (m, 3H), 6.12 – 5.12 (m, 2H), 4.99 (s, 1H), 4.49 – 4.13 (m, 3H), 2.32 – 2.22 (m, 3H).

Example 39: (R)-(7-Cyclohexyl-1H-benzo[d]imidazol-2-yl)(5-methyl-7,8-dihydro-1,6-naphthyridin-6(5H)-yl)methanone



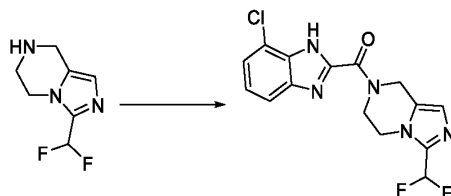
[00278] Step A: To a solution of methyl 7-bromo-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-benzo[d]imidazole-2-carboxylate (product of Example 37, step C) (150 mg, 0.389 mmol) and 2-(cyclohex-1-en-1-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (162 mg, 0.779 mmol) in THF (5.00 mL) and H₂O (1.00 mL) was added K₃PO₄ (248 mg, 1.17 mmol) and Pd(dppf)Cl₂ (57.0 mg, 0.779 mmol) under nitrogen atmosphere. The mixture was stirred at 80 °C for 3 h. The reaction mixture was poured into H₂O (5.00 mL) and extracted with EtOAc (5.00 mL x 3). The combined organic layers were dried over Na₂SO₄, filtered, and concentrated under vacuum to give a residue which was purified by flash silica gel chromatography using a gradient of EtOAc/petroleum ether from 0/1 to 1/3 to afford methyl 7-(cyclohex-1-en-1-yl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-benzo[d]imidazole-2-carboxylate. LC-MS: 387.3 [M+H]⁺.

[00279] Step B: A solution of methyl 7-cyclohexyl-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-benzo[d]imidazole-2-carboxylate (150 mg, 0.388 mmol) and 10% palladium on carbon (150 mg) in EtOAc (20.0 mL) was degassed and purged with hydrogen for three times. The mixture was stirred at 20 °C for 1 h under hydrogen (15 psi). The suspension was filtered through a pad of Celite, and the filter cake was extracted with EtOAc (2.00 mL x 3). The combined filtrates were concentrated under vacuum to give methyl 7-cyclohexyl-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-benzo[d]imidazole-2-carboxylate. LC-MS: 389.3 [M+H]⁺.

[00280] Step C: To a solution of methyl 7-cyclohexyl-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-benzo[d]imidazole-2-carboxylate (100 mg, 0.257 mmol) in EtOH (4.80 mL) was added conc. HCl (1.60 mL). The mixture was stirred at 80 °C for 30 min. The reaction mixture was allowed to cool to room temperature, poured into H₂O (3.00 mL) and extracted with MTBE (5.00 mL x 2). The aqueous layer was acidified to pH 5 with 1M HCl. The product was extracted with DCM (3.00 mL x 5) and the combined organic layers were dried over Na₂SO₄, filtered, and concentrated under vacuum to give 7-cyclohexyl-1H-benzo[d]imidazole-2-carboxylic acid which was used in the next step without any further purification. LC-MS: 245.2 [M+H]⁺.

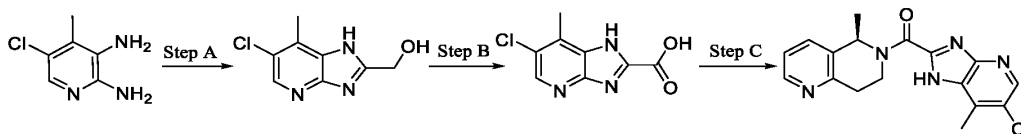
[00281] Step D: To a solution of 7-cyclohexyl-1H-benzo[d]imidazole-2-carboxylic acid (40.0 mg, 0.819 mmol) and (R)-5-methyl-5,6,7,8-tetrahydro-1,6-naphthyridine (30.2 mg, 0.819 mmol) in DCM (3.00 mL) was added TEA (24.9 mg, 0.246 mmol) and T₄P (118 mg, 0.164 mmol). The mixture was stirred at 20 °C for 1 h. The mixture was poured into H₂O (5.00 mL) and extracted with EtOAc (3.00 mL x 3). The combined organic layers were dried over Na₂SO₄, filtered, and concentrated under vacuum to give a residue which was purified by preparative HPLC (Phenomenex Gemini C18 column (150 × 50 mm, 10 μm); flow rate: 25 mL/min; gradient: 50% – 85% B over 8 min; mobile phase A: 10 mM aqueous NH₄HCO₃, mobile phase B: acetonitrile) to afford (R)-(7-cyclohexyl-1H-benzo[d]imidazol-2-yl)(5-methyl-7,8-dihydro-1,6-naphthyridin-6(5H)-yl)methanone. LC-MS: 375.2 [M+H]⁺.

Example 40: (7-Chloro-1H-benzo[d]imidazol-2-yl)(3-(difluoromethyl)-5,6-dihydroimidazo[1,5-a]pyrazin-7(8H)-yl)methanone



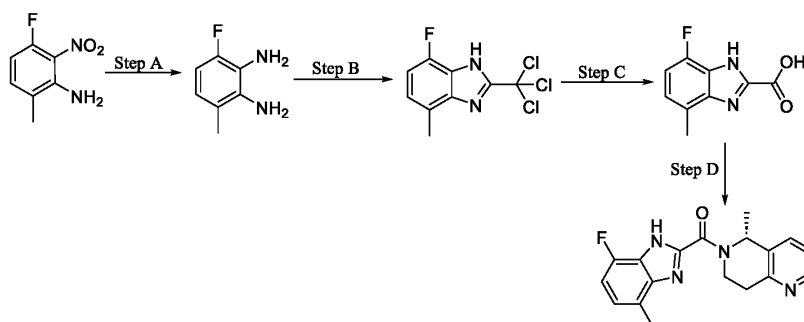
[00282] The title compound was prepared from 3-(difluoromethyl)-5,6,7,8-tetrahydroimidazo[1,5-a]pyrazine and 7-chloro-1H-benzo[d]imidazole-2-carboxylic acid according to the procedure of Example 1, Step A. LC-MS: 352.0 [M+H]⁺. ¹H NMR (400 MHz, DMSO-*d*₆) δ 7.61 – 7.50 (m, 1H), 7.43 – 7.29 (m, 2H), 7.28 – 7.08 (m, 1H), 7.07 – 6.93 (m, 1H), 5.77 – 5.64 (m, 1H), 5.07 – 4.95 (m, 1H), 4.99 (s, 2H), 4.40 – 4.29 (m, 2H), 4.14 (br d, *J* = 4.5 Hz, 1H).

Example 41: (R)-(6-Chloro-7-methyl-3H-imidazo[4,5-b]pyridin-2-yl)(5-methyl-7,8-dihydro-1,6-naphthyridin-6(5H)-yl)methanone



[00283] The title compound was prepared from 5-chloro-4-methylpyridine-2,3-diamine according to the procedure of Example 35, Steps A, B, and C. LC-MS: 342.1 [M+H]⁺. ¹H NMR (400 MHz, DMSO-*d*₆) δ 8.81 – 8.68 (m, 1H), 8.56 (br d, *J* = 7.1 Hz, 1H), 8.51 – 8.42 (m, 1H), 8.00 – 7.74 (m, 1H), 6.67 – 5.83 (m, 1H), 5.56 – 4.74 (m, 2H), 3.88 – 3.03 (m, 3H), 2.66 (s, 3H), 1.93 – 1.48 (m, 3H).

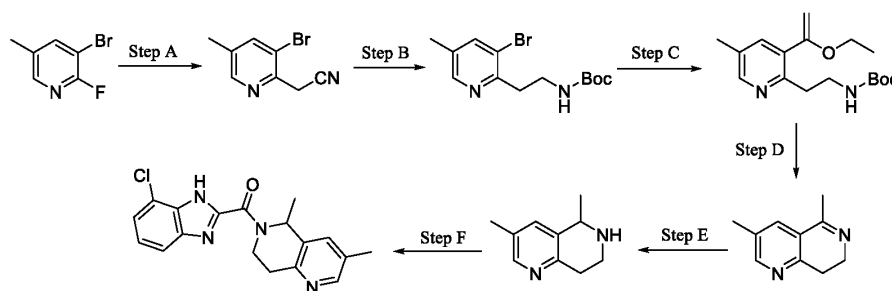
Example 42: (R)-(4-Fluoro-7-methyl-1H-benzo[d]imidazol-2-yl)(5-methyl-7,8-dihydro-1,6-naphthyridin-6(5H)-yl)methanone



[00284] Step A: A solution of 3-fluoro-6-methyl-2-nitroaniline (500 mg, 6.25 mmol) and 10% palladium on carbon (500 mg) in EtOAc (100 mL) was degassed and purged with hydrogen for three times. The mixture was stirred at 20 °C for 1 h under hydrogen (15 psi). The suspension was filtered through a pad of Celite, and the cake was washed with EtOAc (20.0 mL×3). The combined filtrates were concentrated under vacuum to give 3-fluoro-6-methylbenzene-1,2-diamine. LC-MS: 141.3 [M+H]⁺.

[00285] Steps B, C, and D: The title compound was prepared from 3-fluoro-6-methylbenzene-1,2-diamine according to the procedure of Example 30, Steps A, B, and C. LC-MS: 325.1 [M+H]⁺. ¹H NMR (400 MHz, CDCl₃) δ 8.61 (br t, *J* = 5.8 Hz, 1H), 8.33 – 8.15 (m, 1H), 7.82 – 7.58 (m, 1H), 7.14 – 6.96 (m, 2H), 6.70 – 6.52 (m, 1H), 6.15 – 5.06 (m, 1H), 4.03 – 3.27 (m, 3H), 2.57 (d, *J* = 8.8 Hz, 3H), 1.88 – 1.71 (m, 3H).

Example 43: (7-Chloro-1H-benzo[d]imidazol-2-yl)(3,5-dimethyl-7,8-dihydro-1,6-naphthyridin-6(5H)-yl)methanone



[00286] Step A: To a solution of LiHMDS (52.6 mL, 52.6 mmol, 1M) in THF (30.0 mL) was added acetonitrile (2.16 g, 52.6 mmol) at –78 °C dropwise under nitrogen. The mixture was stirred at –78 °C for 1 h. And then 3-bromo-2-fluoro-5-methylpyridine (5.00 g, 26.3 mmol) in THF (30.0 mL) was added at –78 °C dropwise. The mixture was stirred at same temperature for 2 h and then stirred at 20 °C for 12 h under nitrogen. The reaction mixture was poured into H₂O (80.0 mL) and washed with EtOAc (100 mL x 3). The combined organic layers were dried over

Na₂SO₄, filtered, and concentrated under vacuum to give a residue which was purified by flash silica gel chromatography using a gradient of EtOAc/petroleum ether from 0/1 to 1/5 to afford 2-(3-bromo-5-methylpyridin-2-yl)acetonitrile. LC-MS: 211.0 [M+H]⁺.

[00287] Step B: To a solution of Raney Ni (2.20 g) in MeOH (220 mL) was added 2-(3-bromo-5-methylpyridin-2-yl)acetonitrile (2.20 g, 10.4 mmol) and Boc₂O (11.4 g, 52.1 mmol). The mixture was stirred at 20 °C for 6 h under hydrogen. The mixture was filtered through Celite pad, filtered, and concentrated under vacuum to give a residue which was purified by flash silica gel chromatography using a gradient of EtOAc/petroleum ether from 0/1 to 1/5 to afford tert-butyl (2-(3-bromo-5-methylpyridin-2-yl)ethyl)carbamate. LC-MS: 315.2 [M+H]⁺.

[00288] Step C: A mixture of tert-butyl (2-(3-bromo-5-methylpyridin-2-yl)ethyl)carbamate (1.48 g, 4.70 mmol), tributyl(1-ethoxyvinyl)stannane (3.90 g, 10.8 mmol) and Pd(PPh₃)₂Cl₂ (264 mg, 0.376 mmol) in dioxane (30.0 mL) was degassed and purged with nitrogen for 3 times, and then the mixture was stirred at 90 °C for 2 h under nitrogen. The reaction mixture was poured into H₂O (30.0 mL) and washed with EtOAc (30.0 mL x 3). The combined organic layers were dried over Na₂SO₄, filtered, and concentrated under vacuum to give a residue which was purified by flash silica gel chromatography using a gradient of EtOAc/petroleum ether from 0/1 to 1/5 to afford tert-Butyl (2-(3-(1-ethoxyvinyl)-5-methylpyridin-2-yl)ethyl)carbamate. LC-MS: 307.3 [M+H]⁺.

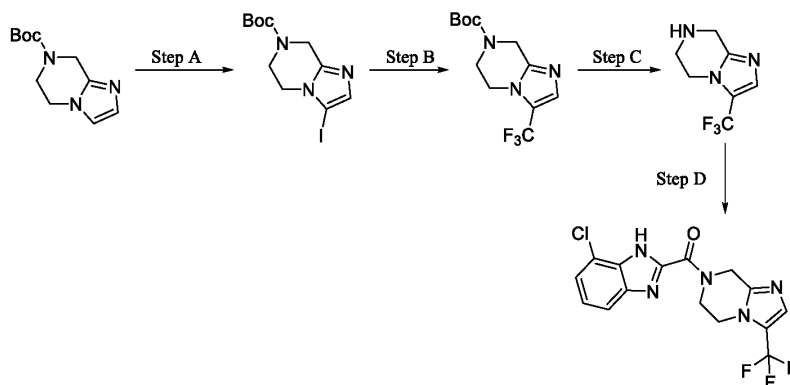
[00289] Step D: To a mixture of tert-butyl (2-(3-(1-ethoxyvinyl)-5-methylpyridin-2-yl)ethyl)carbamate (1.29 g, 4.21 mmol) in EtOAc (1.00 mL) was added HCl/EtOAc (4M, 12.9 mL). The mixture was stirred at 20 °C for 1 h. The reaction mixture was concentrated under vacuum to give 3,5-dimethyl-7,8-dihydro-1,6-naphthyridine. LC-MS: 161.2 [M+H]⁺.

[00290] Step E: To a solution of 3,5-dimethyl-7,8-dihydro-1,6-naphthyridine (200 mg, 1.25 mmol) in MeOH (4.00 mL) was added NaBH₄ (104 mg, 2.75 mmol) at 0 °C under nitrogen. The mixture was stirred at 20 °C for 2 h. The reaction mixture was poured into H₂O (5.00 mL) and washed with DCM (5.00 mL x 3). The combined organic layers were dried over Na₂SO₄, filtered, and concentrated under vacuum to give 3,5-dimethyl-5,6,7,8-tetrahydro-1,6-naphthyridine. LC-MS: 163.3 [M+H]⁺.

[00291] Step F: To a solution of 3,5-dimethyl-5,6,7,8-tetrahydro-1,6-naphthyridine (60.0 mg, 0.370 mmol) and 7-chloro-1H-benzo[d]imidazole-2-carboxylic acid (72.7 mg, 0.370 mmol) in DMF (2.00 mL) was added DIEA (143 mg, 1.11 mmol) and HATU (141 mg, 0.370 mmol). The mixture was stirred at 20 °C for 1 h. The reaction mixture was poured into H₂O (2.00 mL) and washed with EtOAc (3.00 mL x 3). The combined organic layers were dried over Na₂SO₄, filtered, and concentrated under vacuum to give a residue which was purified by preparative

HPLC (Phenomenex Gemini C18 column (75 × 30 mm, 3 μm); flow rate: 60 mL/min; gradient: 5% – 35% B over 8 min; mobile phase A: 0.04% aqueous HCl, mobile phase B: acetonitrile) to afford (7-chloro-1H-benzo[d]imidazol-2-yl)(3,5-dimethyl-7,8-dihydro-1,6-naphthyridin-6(5H)-yl)methanone. LC-MS: 341.1 [M+H]⁺. ¹H NMR (400 MHz, DMSO-*d*₆) δ 8.87 – 8.59 (m, 1H), 8.53 – 8.24 (m, 1H), 7.70 – 7.47 (m, 1H), 7.43 – 7.28 (m, 2H), 6.69 – 5.81 (m, 1H), 5.77 – 4.72 (m, 2H), 3.81 – 3.07 (m, 3H), 2.48 – 2.35 (m, 3H), 1.85 – 1.55 (m, 3H).

Example 44: (7-Chloro-1H-benzo[d]imidazol-2-yl)(3-(trifluoromethyl)-5,6-dihydroimidazo[1,2-a]pyrazin-7(8H)-yl)methanone



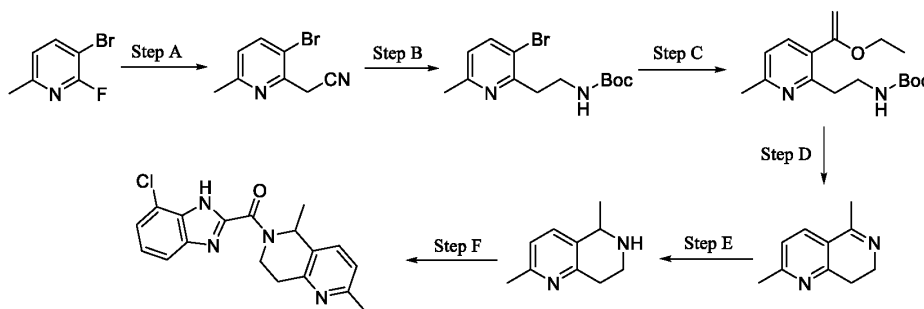
[00292] Step A: To a solution of tert-butyl 5,6-dihydroimidazo[1,2-a]pyrazine-7(8H)-carboxylate (2.00 g, 8.96 mmol) in toluene (40.0 mL) and DMF (10.0 mL) was added NIS (2.12 g, 9.41 mmol). The resulting mixture was stirred at 110 °C for 12 h. The reaction mixture was poured into H₂O (50.0 mL) and extracted with EtOAc (50.0 mL x 2). The combined organic layers were dried over Na₂SO₄, filtered, and concentrated under vacuum to give a residue which was purified by flash silica gel chromatography using a gradient of EtOAc/petroleum ether from 0/1 to 1/1 to afford tert-butyl 3-iodo-5,6-dihydroimidazo[1,2-a]pyrazine-7(8H)-carboxylate. LC-MS: 350.2 [M+H]⁺.

[00293] Step B: A mixture of tert-butyl 3-iodo-5,6-dihydroimidazo[1,2-a]pyrazine-7(8H)-carboxylate (800 mg, 2.29 mmol), methyl 2,2-difluoro-2-fluorosulfonyl-acetate (3.74 g, 19.5 mmol), CuI (3.71 g, 19.5 mmol) in DMF (15.0 mL) was degassed and purged with nitrogen for 3 times, and then the mixture was stirred at 60 °C for 12 h under a nitrogen atmosphere. The reaction mixture was poured into H₂O (20.0 mL) and extracted with EtOAc (30.0 mL x 2). The combined organic layers were dried over Na₂SO₄, filtered, and concentrated under vacuum to give a residue which was purified by flash silica gel chromatography using a gradient of EtOAc/petroleum ether from 0/1 to 1/1 to afford tert-butyl 3-(trifluoromethyl)-5,6-dihydroimidazo[1,2-a]pyrazine-7(8H)-carboxylate. LC-MS: 292.2 [M+H]⁺.

[00294] Step C: A solution of tert-butyl 3-(trifluoromethyl)-5,6-dihydroimidazo[1,2-a]pyrazine-7(8H)-carboxylate (200 mg, 0.687 mmol) in HCl/EtOAc (4M, 2.00 mL) was stirred at 25 °C for 2 h. The mixture was concentrated under vacuum to give a residue which was purified by preparative HPLC (Phenomenex Luna C18 column (75 × 30 mm, 3 μm); flow rate: 25 mL/min; gradient: 1% – 10% B over 8 min; mobile phase A: 0.1% aqueous HCl, mobile phase B: acetonitrile) to afford 3-(trifluoromethyl)-5,6,7,8-tetrahydroimidazo[1,2-a]pyrazine. LC-MS: 192.2 [M+H]⁺.

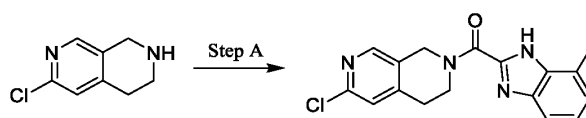
[00295] Step D: A mixture of 3-(trifluoromethyl)-5,6,7,8-tetrahydroimidazo[1,2-a]pyrazine (100 mg, 0.523 mmol), 7-chloro-1H-benzimidazole-2-carboxylic acid (103 mg, 0.523 mmol), HATU (199 mg, 0.523 mmol) and DIEA (203 mg, 1.57 mmol) in DMF (2.00 mL) was stirred at 25 °C for 1 h. The mixture was stirred at 25 °C for 1 h. The reaction mixture was poured into H₂O (2.00 ml) and extracted with EtOAc (2.00 ml × 3). The combine organic layers were dried over Na₂SO₄, filtered and concentrated under vacuum to give a residue which was purified by preparative HPLC (Phenomenex Luna C18 column (75 × 30 mm, 3 μm); flow rate: 25 mL/min; gradient: 30% – 60% B over 8 min; mobile phase A: 0.04% aqueous HCl mobile phase B: acetonitrile) to afford (7-chloro-1H-benzo[d]imidazol-2-yl)(3-(trifluoromethyl)-5,6-dihydroimidazo[1,2-a]pyrazin-7(8H)-yl)methanone. LC-MS: 370.1 [M+H]⁺. ¹H NMR (400 MHz, CDCl₃) δ 7.75 - 7.63 (m, 2H), 7.36 (br s, 2H), 5.70 - 5.16 (m, 4H), 4.64 (br s, 2H).

Example 45: (7-Chloro-1H-benzo[d]imidazol-2-yl)(2,5-dimethyl-7,8-dihydro-1,6-naphthyridin-6(5H)-yl)methanone



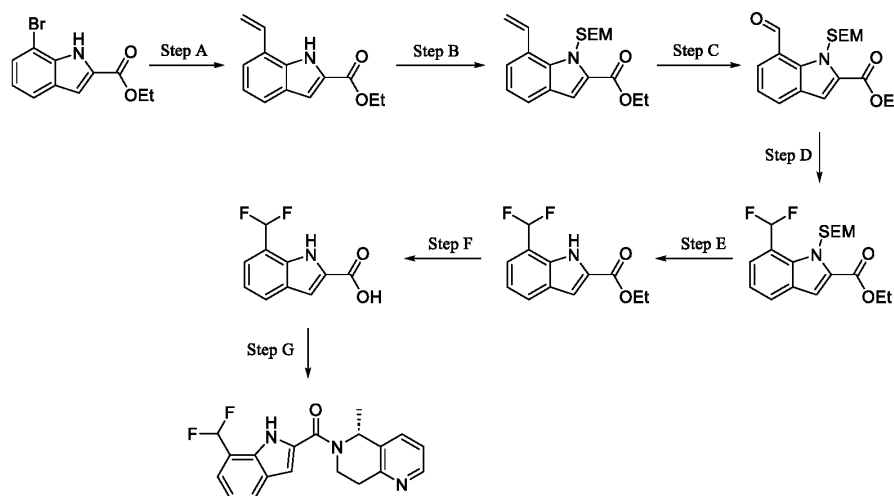
[00296] The title compound was prepared from 3-bromo-2-fluoro-6-methylpyridine according to the procedure of Example 43, Steps A, B, C, D, E, and F. LC-MS: 342.1 [M+H]⁺. ¹H NMR (400 MHz, DMSO-*d*₆) δ 8.60 – 8.29 (m, 1H), 7.88 – 7.68 (m, 1H), 7.62 – 7.50 (m, 1H), 7.45 – 7.26 (m, 2H), 6.71 – 5.83 (m, 1H), 5.78 – 4.73 (m, 2H), 3.76 – 3.16 (m, 3H), 2.84 – 2.65 (m, 3H), 1.85 – 1.44 (m, 3H).

Example 46: (6-Chloro-3,4-dihydro-2,7-naphthyridin-2(1H)-yl)(7-methyl-1H-benzo[d]imidazol-2-yl)methanone



[00297] Step A: A mixture of 6-chloro-1,2,3,4-tetrahydro-2,7-naphthyridine (35.0 mg, 0.207 mmol), 7-methyl-1H-benzimidazole-2-carboxylic acid (36.0 mg, 0.207 mmol), TEA (63.0 mg, 0.622 mmol) and T₄P (249 mg, 0.415 mmol, 50% purity) in DCM (1.00 mL) was stirred at 20 °C for 1 h. The mixture was concentrated under vacuum at 30 °C to give a residue which was purified by preparative HPLC (Phenomenex Luna C18 column 75×30mm×3μm); flow rate: 25 mL/min; gradient: 30% – 60% B over 8 min; mobile phase A: 0.04% aqueous HCl, mobile phase B: acetonitrile) to afford (6-chloro-3,4-dihydro-2,7-naphthyridin-2(1H)-yl)(7-methyl-1H-benzo[d]imidazol-2-yl)methanone. LC-MS: 327.1 [M+H]⁺. ¹H NMR (400 MHz, CDCl₃) δ 8.30 – 8.09 (m, 1H), 7.75 – 7.61 (m, 1H), 7.44 – 7.27 (m, 2H), 7.18 – 7.06 (m, 1H), 5.62 – 5.32 (m, 1H), 4.75 – 4.43 (m, 1H), 4.31 – 4.07 (m, 1H), 4.00 – 3.70 (m, 1H), 3.18 – 3.01 (m, 1H), 2.99 – 2.82 (m, 1H), 2.73 – 2.63 (m, 3H).

Example 47: (R)-(7-(Difluoromethyl)-1H-indol-2-yl)(5-methyl-7,8-dihydro-1,6-naphthyridin-6(5H)-yl)methanone



[00298] Step A: To a solution of ethyl 7-bromo-1H-indole-2-carboxylate (5.00 g, 18.7 mmol) and 4,4,5,5-tetramethyl-2-vinyl-1,3,2-dioxaborolane (7.18 g, 46.6 mmol) in dioxane (100 mL) and H₂O (10.0 mL) was added Na₂CO₃ (4.55 mg, 42.9 mmol) and Pd(dppf)Cl₂ (1.52 g, 1.86 mmol). The mixture was degassed and purged with nitrogen three times and stirred at 80 °C for 10 h under nitrogen. The reaction mixture was allowed to cool to room temperature, poured into water (100 mL) and extracted with EtOAc (80.0 mL × 2). The combined organic layers were dried over Na₂SO₄, filtered, and concentrated under vacuum to give a residue which was purified

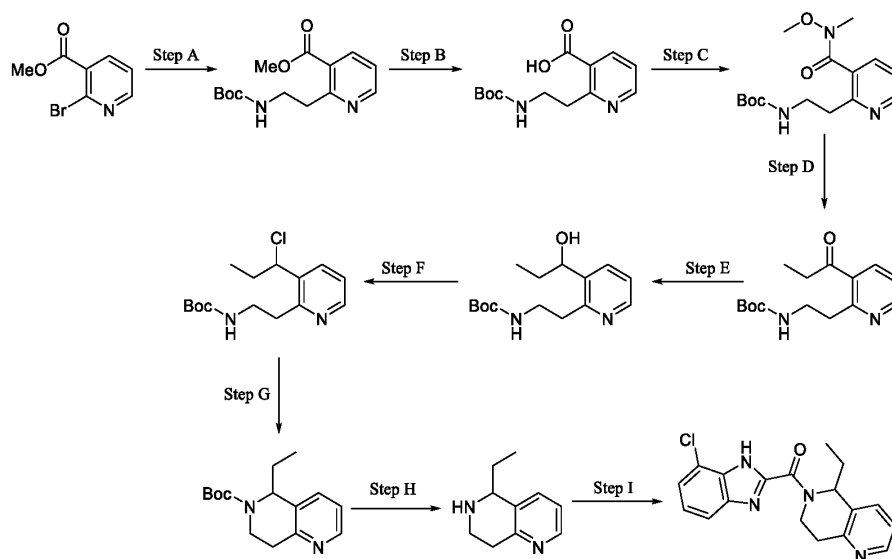
by flash silica gel chromatography using a gradient of EtOAc/petroleum ether from 0/1 to 1/20 to afford ethyl 7-vinyl-1H-indole-2-carboxylate. LC-MS: 216.1 [M+H]⁺.

[00299] Step B: A mixture of ethyl 7-vinyl-1H-indole-2-carboxylate (850 mg, 3.95 mmol) in NMP (12.0 mL) at 0 °C was degassed and purged with nitrogen. To the mixture was added NaH (316 mg, 7.95 mmol, 60% purity) and the resulting mixture was stirred at 0 °C for 0.5 h, followed by SEM-Cl (658 mg, 3.95 mmol) and purged with nitrogen three times, then stirred at 20 °C for 1 h under nitrogen. The mixture was poured into water (12.0 mL) and extracted with EtOAc (12.0 mL x 3). The combined organic layers were dried over Na₂SO₄, filtered, and concentrated under vacuum to give a residue which was purified by flash silica gel chromatography using a gradient of EtOAc/petroleum ether from 0/1 to 1/20 to afford ethyl 1-((2-(trimethylsilyl)ethoxy)methyl)-7-vinyl-1H-indole-2-carboxylate. LC-MS: 228.1 [M+H]⁺.

[00300] Step C: A mixture of ethyl 1-((2-(trimethylsilyl)ethoxy)methyl)-7-vinyl-1H-indole-2-carboxylate (440 mg, 1.27 mmol) in THF (1.00 mL) and H₂O (1.00 mL) was cooled to 0 °C. The mixture was degassed and purged with nitrogen three times. To the mixture was added OsO₄ (1.25 g, 0.255 mmol) and the resulting mixture was stirred at 0 °C for 1 h. To the mixture was added NaIO₄ (1.36 g, 6.37 mmol) and purged with nitrogen three times, then stirred at 20 °C for 12 h under nitrogen. The mixture was poured into water (50.0 mL) and extracted with EtOAc (50.0 mL x 5). The combined organic layers were dried over Na₂SO₄, filtered, and concentrated under vacuum to give a residue which was purified by flash silica gel chromatography using a gradient of EtOAc/petroleum ether from 0/1 to 1/20 to afford ethyl 7-formyl-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-indole-2-carboxylate. LC-MS: 230.1 [M+H]⁺.

[00301] Steps D, E, F, and G: (R)-(7-(Difluoromethyl)-1H-indol-2-yl)(5-methyl-7,8-dihydro-1,6-naphthyridin-6(5H)-yl)methanone was prepared from ethyl 7-formyl-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-indole-2-carboxylate according to the procedure of Example 37, Steps E, F, G, and H. LC-MS: 342.1 [M+H]⁺. ¹H NMR (400 MHz, CDCl₃) δ 9.49 (br s, 1H), 8.62 (br d, *J* = 3.8 Hz, 1H), 8.21 (br d, *J* = 7.0 Hz, 1H), 7.96 – 7.66 (m, 2H), 7.38 (d, *J* = 7.0 Hz, 1H), 7.26 – 7.19 (m, 1H), 7.12 – 6.71 (m, 2H), 5.97 (q, *J* = 6.5 Hz, 1H), 4.97 (br d, *J* = 7.6 Hz, 1H), 4.14 – 3.88 (m, 1H), 3.80 – 3.45 (m, 2H), 1.75 (br d, *J* = 5.5 Hz, 3H).

Example 48: (7-Chloro-1H-benzo[d]imidazol-2-yl)(5-ethyl-7,8-dihydro-1,6-naphthyridin-6(5H)-yl)methanone



[00302] Step A: To a mixture of methyl 2-bromonicotinate (1.80 g, 8.33 mmol) and potassium (2-((tert-butoxycarbonyl)amino)ethyl)trifluoroborate (2.30 g, 9.17 mmol) in H₂O (15.0 mL) and toluene (45.0 mL) was added Pd(dppf)Cl₂ (610 mg, 0.833 mmol) and Cs₂CO₃ (8.14 g, 25.0 mmol). The mixture was degassed and purged with nitrogen three times and stirred at 80 °C for 12 h under a nitrogen atmosphere. The reaction mixture was poured into H₂O (100 mL) and extracted with EtOAc (40.0 mL x 3). The combined organic layers were dried over Na₂SO₄, filtered, and concentrated under vacuum to give a residue which was purified by flash silica gel chromatography using a gradient of EtOAc/petroleum ether from 0/1 to 1/7 to afford methyl 2-((tert-butoxycarbonyl)amino)ethylnicotinate. LC-MS: 281.3 [M+H]⁺.

[00303] Step B: To a solution of methyl 2-((tert-butoxycarbonyl)amino)ethylnicotinate (1.45 g, 5.17 mmol) in dioxane (10.0 mL) was added NaOH aqueous (2M, 1.5 mL), then the mixture was stirred at 25 °C for 1 h. The reaction mixture was added to H₂O (15.0 mL) and extracted with MTBE (5.00 mL x 3). The aqueous phase was neutralized to pH 5 - 4 using 1M HCl and then the precipitate was filtered. The reaction mixture was filtered and the filter cake was washed with H₂O (1.00 mL x 2), dried in vacuum to give 2-((tert-butoxycarbonyl)amino)ethylnicotinic acid. LC-MS: 267.2 [M+H]⁺.

[00304] Step C: A mixture of 2-((tert-butoxycarbonyl)amino)ethylnicotinic acid (1.15 g, 4.32 mmol), N-methoxymethanamine (463 mg, 4.75 mmol, HCl salt), HATU (821 mg, 2.16 mmol) and DIEA (1.50 mL, 8.64 mmol) in DMF (20.0 mL) was stirred at 20 °C for 1 h. The reaction mixture was poured into H₂O (20.0 mL) and extracted with DCM (10.0 mL x 3). The combined organic layers were dried over Na₂SO₄, filtered, and concentrated under vacuum to give a residue which was purified by flash silica gel chromatography using a gradient of

EtOAc/petroleum ether from 0/1 to 1/1 to afford tert-butyl (2-(3-

(methoxy(methyl)carbamoyl)pyridin-2-yl)ethyl)carbamate. LC-MS: 310.2 [M+H]⁺.

[00305] Step D: To a solution of tert-butyl (2-(3-(methoxy(methyl)carbamoyl)pyridin-2-yl)ethyl)carbamate (400 mg, 1.29 mmol) in THF (15.0 mL) was added EtMgBr (3 M, 1.30 mL) at 0 °C. The mixture was stirred at 20 °C for 5 h. The reaction mixture was poured into H₂O (15.0 mL) and extracted with EtOAc (5.00 mL x 3). The combined organic layers were dried over Na₂SO₄, filtered, and concentrated under vacuum to give a residue which was purified by flash silica gel chromatography using a gradient of EtOAc/petroleum ether from 0/1 to 1/1 to afford tert-butyl (2-(3-propionylpyridin-2-yl)ethyl)carbamate. LC-MS: 279.3 [M+H]⁺.

[00306] Step E: To a solution of tert-butyl (2-(3-propionylpyridin-2-yl)ethyl)carbamate (70.0 mg, 0.251 mmol) in MeOH (2.00 mL) was added NaBH₄ (14.3 mg, 0.377 mmol) at 0 °C. The mixture was stirred at 20 °C for 2 h. The reaction mixture was poured into H₂O (2.00 mL) and extracted with EtOAc (1.00 mL x 3). The combined organic layers were dried over Na₂SO₄, filtered, and concentrated under vacuum to give tert-butyl (2-(3-(1-hydroxypropyl)pyridin-2-yl)ethyl)carbamate. LC-MS: 281.2 [M+H]⁺.

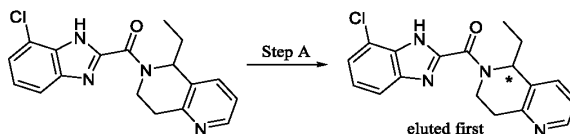
[00307] Step F: To a solution of tert-butyl (2-(3-(1-hydroxypropyl)pyridin-2-yl)ethyl)carbamate (80.0 mg, 0.285 mmol) in DCM (2.00 mL) was added TEA (59.6 µL, 0.428 mmol), followed by MsCl (65.4 mg, 0.571 mmol) at 0 °C under a Nitrogen atmosphere. The resulting reaction mixture was stirred at 20 °C for 2 h. The reaction mixture was poured into H₂O (2.00 mL) and extracted with DCM (1.00 mL x 3). The combined organic layers were dried over Na₂SO₄, filtered, and concentrated under vacuum to give a residue, which was purified by preparative TLC (EtOAc, R_f = 0.4 and 0.3) to afford tert-butyl (2-(3-(1-chloropropyl)pyridin-2-yl)ethyl)carbamate. LC-MS: 299.2 [M+H]⁺.

[00308] Step G: To a solution of tert-butyl (2-(3-(1-chloropropyl)pyridin-2-yl)ethyl)carbamate (20.0 mg, 0.067 mmol) in DMF (0.50 mL) was added t-BuONa (12.9 mg, 0.134 mmol) and KI (1.11 mg, 0.007 mmol). The mixture was stirred at 100 °C for 0.5 h. The reaction mixture was poured into H₂O (1.00 mL) and extracted with EtOAc (1.00 mL x 3). The combined organic layers were dried over Na₂SO₄, filtered, and concentrated under vacuum to give tert-butyl 5-ethyl-7,8-dihydro-1,6-naphthyridine-6(5H)-carboxylate. LC-MS: 263.3 [M+H]⁺.

[00309] Step H: To a solution of tert-butyl 5-ethyl-7,8-dihydro-1,6-naphthyridine-6(5H)-carboxylate (45.0 mg, 0.172 mmol) in EtOAc (0.50 mL) was added HCl/EtOAc (4M, 1.00 mL). The resulting mixture was stirred at 20 °C for 1 h. The mixture was concentrated under vacuum to give 5-ethyl-5,6,7,8-tetrahydro-1,6-naphthyridine. LC-MS: 163.3 [M+H]⁺.

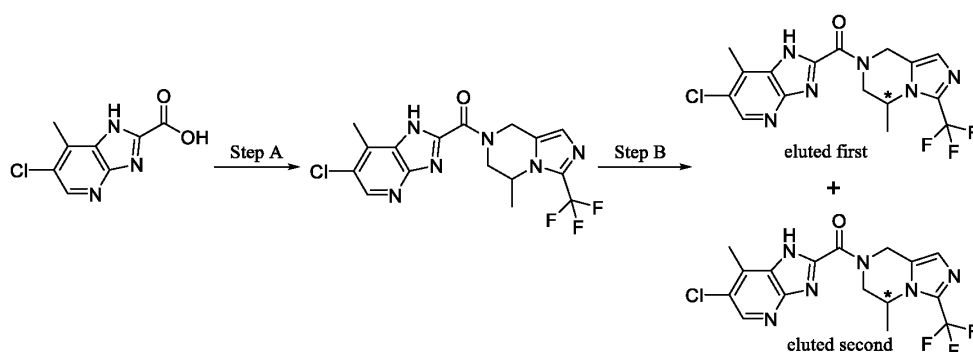
[00310] Step I: A mixture of 5-ethyl-5,6,7,8-tetrahydro-1,6-naphthyridine (30.0 mg, 0.151 mmol, HCl salt), 7-chloro-1H-benzo[d]imidazole-2-carboxylic acid (29.7 mg, 0.151 mmol), HATU (28.7 mg, 0.075 mmol) and DIEA (0.039 mL, 0.226 mmol) in DMF (1.00 mL) was stirred at 20 °C for 1 h. The reaction mixture was poured into H₂O (2.00 mL) and extracted with EtOAc (1.00 mL x 3). The combined organic layers were dried over Na₂SO₄, filtered, and concentrated under vacuum to give a residue which was purified by preparative HPLC (Phenomenex Luna C18 column (80 × 30 mm, 3 μm); flow rate: 25 mL/min; gradient: 10% – 40% B over 8 min; mobile phase A: 0.04% aqueous HCl, mobile phase B: acetonitrile) to afford (7-chloro-1H-benzo[d]imidazol-2-yl)(5-ethyl-7,8-dihydro-1,6-naphthyridin-6(5H)-yl)methanone. LC-MS: 341.1 [M+H]⁺. ¹H NMR (400 MHz, DMSO-d₆) δ 8.84 – 8.69 (m, 1H), 8.64 – 8.45 (m, 1H), 7.97 – 7.82 (m, 1H), 7.62 – 7.50 (m, 1H), 7.45 – 7.29 (m, 2H), 6.96 – 5.86 (m, 1H), 5.81 – 4.70 (m, 1H), 3.79 – 3.65 (m, 1H), 3.34 – 3.22 (m, 2H), 2.07 – 1.91 (m, 2H), 1.07 – 0.93 (m, 3H).

Example 48A: (R) or (S)-(7-Chloro-1H-benzo[d]imidazol-2-yl)(5-ethyl-7,8-dihydro-1,6-naphthyridin-6(5H)-yl)methanone (single enantiomer)



[00311] Step A: (7-Chloro-1H-benzo[d]imidazol-2-yl)(5-ethyl-7,8-dihydro-1,6-naphthyridin-6(5H)-yl)methanone (8.00 mg, 0.024 mmol) was separated by SFC separation((DAICEL CHIRALCEL OZ (250 × 30 mm, 10 μm); flow rate: 64 mL/min; gradient: 45% B over 4 min; mobile phase A: CO₂, mobile phase B: MeOH(0.1%NH₃H₂O)) to afford (R) or (S)-(7-chloro-1H-benzo[d]imidazol-2-yl)(5-ethyl-7,8-dihydro-1,6-naphthyridin-6(5H)-yl)methanone (first eluent). LC-MS: 341.1 [M+H]⁺. ¹H NMR (400 MHz, CDCl₃) δ 11.05 – 10.41 (m, 1H), 8.49 (br d, *J* = 0.8 Hz, 1H), 7.85 – 7.30 (m, 3H), 7.23 (br d, *J* = 5.3 Hz, 1H), 5.83 (br t, *J* = 7.3 Hz, 1H), 5.11 – 2.99 (m, 3H), 2.01 (dt, *J* = 7.0, 14.1 Hz, 2H), 1.35 – 0.92 (m, 5H). The absolute stereochemistry of Example 48A was not determined.

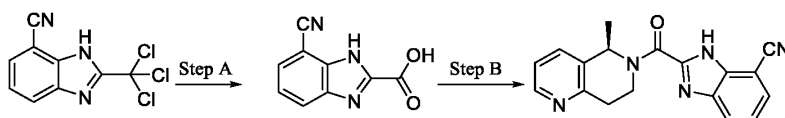
Examples 49A and 49B: (R) or (S)-(6-Chloro-7-methyl-1H-imidazo[4,5-b]pyridin-2-yl)(5-methyl-3-(trifluoromethyl)-5,6-dihydroimidazo[1,5-a]pyrazin-7(8H)-yl)methanone and (R) or (S)-(6-Chloro-7-methyl-1H-imidazo[4,5-b]pyridin-2-yl)(5-methyl-3-(trifluoromethyl)-5,6-dihydroimidazo[1,5-a]pyrazin-7(8H)-yl)methanone



[00312] Step A: Racemic (6-chloro-7-methyl-1H-imidazo[4,5-b]pyridin-2-yl)(5-methyl-3-(trifluoromethyl)-5,6-dihydroimidazo[1,5-a]pyrazin-7(8H)-yl)methanone was prepared from 5-methyl-3-(trifluoromethyl)-5,6,7,8-tetrahydroimidazo[1,5-a]pyrazine and 6-chloro-7-methyl-1H-imidazo[4,5-b]pyridine-2-carboxylic acid according to the procedure of Example 1, Step A. LC-MS: 399.2 $[M+H]^+$.

[00313] Step B: Racemic (6-Chloro-7-methyl-1H-imidazo[4,5-b]pyridin-2-yl)(5-methyl-3-(trifluoromethyl)-5,6-dihydroimidazo[1,5-a]pyrazin-7(8H)-yl)methanone (71.0 mg, 0.178 mmol) was further purified by SFC separation((Phenomenex-Cellulose-2 (250 × 30 mm, 10 μ m); flow rate: 70 mL/min; gradient: 30 – 30% B over 11 min; mobile phase A: CO₂, mobile phase B: EtOH(0.1%NH₃H₂O)) to afford a first eluted compound and a second eluted compound. First eluted compound (**Example 49A**): LC-MS: 399.1 $[M+H]^+$. ¹H NMR (400 MHz, DMSO-*d*₆) δ 14.13 – 13.84 (m, 1H), 8.46 (s, 1H), 7.27 – 6.90 (m, 1H), 6.43 – 5.66 (m, 1H), 5.54 – 4.42 (m, 3H), 3.95 – 3.50 (m, 1H), 2.88 – 2.55 (m, 3H), 1.54 – 1.32 (m, 3H). Second eluted compound (**Example 49B**): LC-MS: 399.1 $[M+H]^+$. ¹H NMR (400 MHz, DMSO-*d*₆) δ 8.28 (s, 1H), 7.23 – 6.82 (m, 1H), 6.20 – 5.54 (m, 1H), 5.46 – 4.49 (m, 3H), 3.85 – 3.44 (m, 1H), 2.60 (s, 3H), 1.40 (d, *J* = 6.5 Hz, 3H). The absolute stereochemistry for the first and second eluted compounds was not determined.

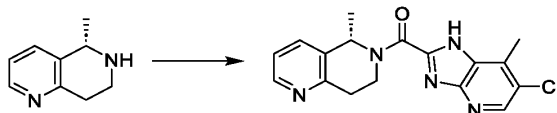
Example 50: (R)-2-(5-Methyl-5,6,7,8-tetrahydro-1,6-naphthyridine-6-carbonyl)-1H-benzo[*d*]imidazole-7-carbonitrile



[00314] (R)-2-(5-Methyl-5,6,7,8-tetrahydro-1,6-naphthyridine-6-carbonyl)-1H-benzo[*d*]imidazole-7-carbonitrile was prepared from 2-(trichloromethyl)-3H-benzimidazole-4-carbonitrile according to the procedure of Example 30, Steps B and C. LC-MS: 318.2 $[M+H]^+$. ¹H NMR (400 MHz, DMSO-*d*₆) δ 13.56 – 13.97 (m, 1 H), 8.36 – 8.48 (m, 1 H), 7.92 (br d, *J* =

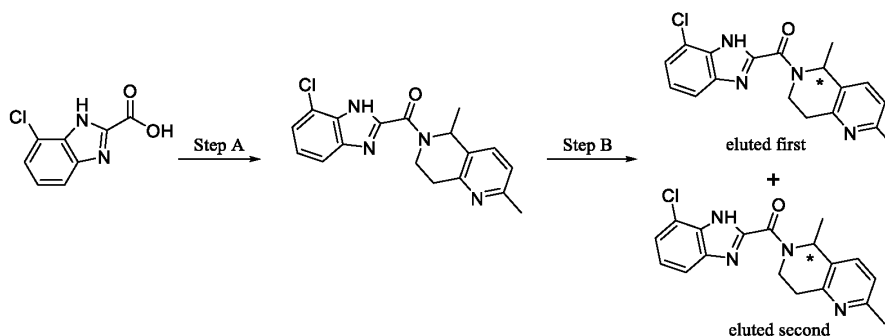
7.75 Hz, 1 H), 7.61 – 7.85 (m, 2 H), 7.41 – 7.55 (m, 1 H), 7.18 – 7.34 (m, 1 H), 5.66 – 6.42 (m, 1 H), 4.58 – 5.55 (m, 1 H), 3.40 – 3.79 (m, 1 H), 3.12 – 3.25 (m, 1 H), 2.94 – 3.01 (m, 1 H), 1.47 – 1.78 (m, 3 H).

Example 51: (S)-(6-Chloro-7-methyl-1H-imidazo[4,5-b]pyridin-2-yl)(5-methyl-7,8-dihydro-1,6-naphthyridin-6(5H)-yl)methanone



[00315] The title compound was prepared from 3-methyl-5,6,7,8-tetrahydroimidazo[1,5-a]pyrazine and 4-chloro-1H-benzimidazole-2-carboxylic acid according to the procedure of Example 3, Step A. LC-MS: 342.0 [M+H]⁺. ¹H NMR (400 MHz, DMSO-*d*₆) δ ppm 8.41 – 8.67 (m, 2 H), 8.00 – 8.22 (m, 1 H), 7.46 – 7.62 (m, 1 H), 5.76 – 6.52 (m, 1 H), 4.71 – 5.48 (m, 1 H), 3.24 – 3.86 (m, 2 H), 3.06 – 3.17 (m, 1 H), 2.66 (s, 3 H), 1.57 – 1.78 (m, 3 H).

Examples 52A and 52B: (R) or (S)-(7-Chloro-1H-benzo[d]imidazol-2-yl)(2,5-dimethyl-7,8-dihydro-1,6-naphthyridin-6(5H)-yl)methanone and (R) or (S)-(7-Chloro-1H-benzo[d]imidazol-2-yl)(2,5-dimethyl-7,8-dihydro-1,6-naphthyridin-6(5H)-yl)methanone

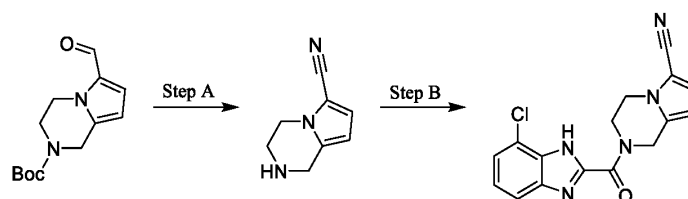


[00316] Step A: Racemic (7-chloro-1H-benzo[d]imidazol-2-yl)(2,5-dimethyl-7,8-dihydro-1,6-naphthyridin-6(5H)-yl)methanone was prepared from 2,5-dimethyl-5,6,7,8-tetrahydro-1,6-naphthyridine and 7-chloro-1H-benzo[d]imidazole-2-carboxylic acid according to the procedure of Example 1, Step A. LC-MS: 341.2 [M+H]⁺.

[00317] Step B: Racemic (7-chloro-1H-benzo[d]imidazol-2-yl)(2,5-dimethyl-7,8-dihydro-1,6-naphthyridin-6(5H)-yl)methanone (170 mg) was purified by SFC separation ((Phenomenex - Cellulose-2(250 × 30 mm, 10 μm); flow rate: 70 mL/min; gradient: 40 – 40% B over 11 min; mobile phase A: CO₂, mobile phase B: EtOH(0.1% NH₃H₂O)) to afford a first eluted compound and a second eluted compound. First eluted compound (**Example 52A**): LC-MS: 341.1 [M+H]⁺. ¹H NMR (400 MHz, DMSO-*d*₆) δ 13.78 – 13.17 (m, 1H), 7.66 (d, *J* = 8.0 Hz, 1H), 7.52 (br d, *J* = 7.9 Hz, 1H), 7.42 – 7.25 (m, 2H), 7.19 – 7.01 (m, 1H), 6.52 – 5.46 (m, 1H), 3.82 – 3.33 (m, 2H),

3.22 – 2.82 (m, 2H), 2.46 – 2.36 (m, 3H), 1.72 – 1.48 (m, 3H). Second eluted compound (**Example 52B**): LC-MS: 341.1 [M+H]⁺. ¹H NMR (400 MHz, DMSO-*d*₆) δ 13.70 – 13.34 (m, 1H), 7.66 (d, *J* = 8.0 Hz, 1H), 7.52 (br d, *J* = 7.9 Hz, 1H), 7.42 – 7.27 (m, 2H), 7.20 – 7.03 (m, 1H), 6.55 – 5.47 (m, 1H), 3.69 (br d, *J* = 1.0 Hz, 2H), 3.26 – 2.83 (m, 2H), 2.47 – 2.36 (m, 3H), 1.74 – 1.41 (m, 3H). The absolute stereochemistry for the first and second eluted compounds was not determined.

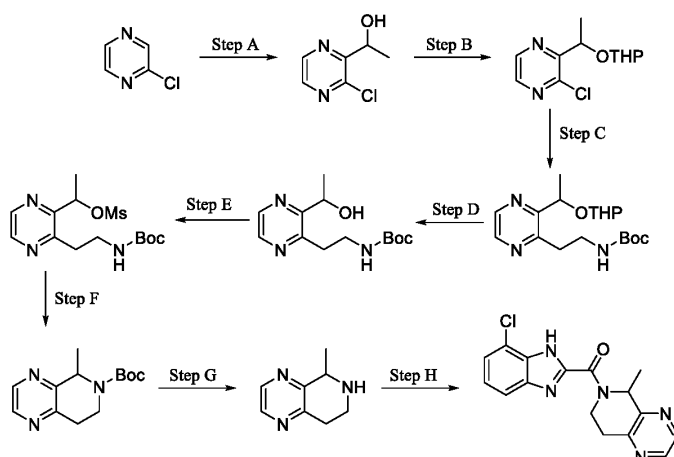
Example 53: 2-(7-Chloro-1H-benzo[d]imidazole-2-carbonyl)-1,2,3,4-tetrahydropyrrolo[1,2-a]pyrazine-6-carbonitrile



[00318] Step A: To a solution of tert-butyl 6-formyl-3,4-dihydro-1H-pyrrolo[1,2-a]pyrazine-2-carboxylate (300 mg, 1.20 mmol) in H₂O (2.00 mL) and EtOH (2.00 mL) was added NH₂OSO₃H (135 mg, 1.20 mmol). The mixture was stirred at 80 °C for 1 h. The solvent was removed in vacuum to give a residue, which was dissolved in DMF (5.00 mL), and the resulting solution was purified by prep-HPLC (column: Phenomenex luna C18 80 × 40mm × 3 μm; mobile phase: [H₂O (0.1% TFA)-ACN]; gradient: 1% - 5% B over 8.0 min) to afford 1,2,3,4-tetrahydropyrrolo[1,2-a]pyrazine-6-carbonitrile. LC-MS: 148.3 [M+H]⁺.

[00319] Step B: To a solution of 7-chloro-1H-benzimidazole-2-carboxylic acid (80.1 mg, 0.407 mmol) in DCM (2.00 mL) were added TEA (123 mg, 1.20 mmol) and BOP-Cl (155 mg, 0.611 mmol) at 0 °C and the resulting mixture was stirred at 0 °C for 1h, then 1,2,3,4-tetrahydropyrrolo[1,2-a]pyrazine-6-carbonitrile (60.0 mg, 0.407 mmol) was added. The resulting mixture was stirred at 20 °C for 12 h. The solvent was removed in vacuum to give a residue, which was dissolved in DMF (5.00 mL), and the resulting solution was purified by prep-HPLC (neutral condition, column: Waters Xbridge BEH C18 100 × 30mm × 10 μm; mobile phase: [H₂O (10mM NH₄HCO₃)-ACN]; gradient: 35% - 65% B over 8.0 min) to afford 2-(7-chloro-1H-benzimidazole-2-carbonyl)-3,4-dihydro-1H-pyrrolo[1,2-a]pyrazine-6-carbonitrile. LC-MS: 326.0 [M+H]⁺. ¹H NMR (400 MHz, DMSO-*d*₆) δ 7.55 (br d, *J* = 8.13 Hz, 1 H), 7.26 – 7.35 (m, 2 H), 6.96 – 7.02 (m, 1 H), 6.00 – 6.29 (m, 1 H), 5.65 (s, 1 H), 4.72 – 5.06 (m, 3 H), 4.14 – 4.28 (m, 3 H).

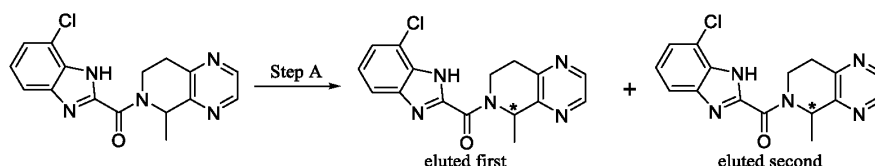
Example 54: (7-Chloro-1H-benzo[d]imidazol-2-yl)(5-methyl-7,8-dihydropyrido[3,4-b]pyrazin-6(5H)-yl)methanone



[00320] Step A: 2,2,6,6-Tetramethylpiperidine (9.18 g, 65.0 mmol) was dissolved in THF (100 mL) and cooled to -78°C . $n\text{-BuLi}$ (2.5 M, 25.0 mL) was added dropwise to keep the temperature below -70°C . The mixture was stirred at -78°C for 30 min under N_2 atmosphere. 2-Chloropyrazine (5.73 g, 50.0 mmol) was added dropwise and the mixture was stirred for 1 h. After this time, acetaldehyde (5M, 20.0 mL) was added and the mixture was allowed to warm to 20°C and stirred for another 4 h under N_2 atmosphere. The reaction mixture was poured into H_2O (50.0 mL) and extracted with DCM (50.0 mL $\times$ 4). The combined organic layers were dried over Na_2SO_4 , filtered, and concentrated under vacuum to give a residue which was purified by flash silica gel chromatography using a gradient of EtOAc/petroleum ether from 1/100 to 1/3 to afford 1-(3-chloropyrazin-2-yl)ethan-1-ol. ^1H NMR (400 MHz, CDCl_3) δ 8.50 (d, $J = 2.5$ Hz, 1H), 8.35 (d, $J = 2.4$ Hz, 1H), 5.28 – 5.11 (m, 1H), 1.53 (d, $J = 6.5$ Hz, 3H).

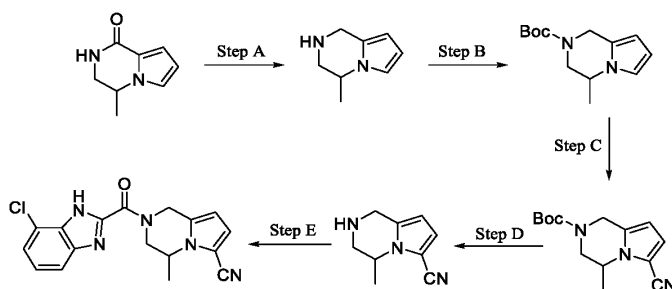
[00321] Steps B, C, D, E, F, G, and H: (7-Chloro-1H-benzimidazol-2-yl)-(5-methyl-7,8-dihydro-5H-pyrido[3,4-b]pyrazin-6-yl)methanone was prepared from 1-(3-chloropyrazin-2-yl)ethan-1-ol according to the procedure of Example 11, Steps B, C, D, E, F, G, and H. LC-MS: 328.1 $[\text{M}+\text{H}]^+$. ^1H NMR (400 MHz, CDCl_3) δ 8.60 – 8.40 (m, 2H), 7.75 – 7.29 (m, 3H), 6.53 – 4.97 (m, 2H), 3.79 – 3.15 (m, 3H), 1.92 – 1.70 (m, 3H).

Examples 54A and 54B: (R) or (S)-(7-Chloro-1H-benzo[d]imidazol-2-yl)(5-methyl-7,8-dihydropyrido[3,4-b]pyrazin-6(5H)-yl)methanone and (R) or (S)-(7-Chloro-1H-benzo[d]imidazol-2-yl)(5-methyl-7,8-dihydropyrido[3,4-b]pyrazin-6(5H)-yl)methanone



[00322] Step A: (7-Chloro-1H-benzo[d]imidazol-2-yl)(5-methyl-7,8-dihydropyrido[3,4-b]pyrazin-6 (5H)-yl)methanone (50.0 mg, 0.153 mmol) was further separated by SFC separation (Phenomenex-DAICEL CHIRALPAK AD (250 × 30 mm, 10 μm); flow rate: 30 mL/min; gradient: 50% B over 14 min; mobile phase A: heptane, mobile phase B: EtOH (0.1% NH₃H₂O) to afford a first eluted compound and a second eluted compound. First eluted compound (**Example 54A**): LC-MS: 328.1 [M+H]⁺. ¹H NMR (400 MHz, CDCl₃) δ 10.88 – 10.33 (m, 1H), 8.61 – 8.33 (m, 2H), 7.84 – 7.28 (m, 3H), 6.68 – 6.36 (m, 1H), 5.98 – 4.93 (m, 1H), 3.82 – 3.02 (m, 3H), 2.00 – 1.68 (m, 3H). Second eluted compound (**Example 54B**): LC-MS: 328.1 [M+H]⁺. ¹H NMR (400 MHz, CDCl₃) δ 10.76 – 10.29 (m, 1H), 8.56 – 8.35 (m, 2H), 7.86 – 7.28 (m, 3H), 6.64 – 6.30 (m, 1H), 6.07 – 4.88 (m, 1H), 3.92 – 2.93 (m, 3H), 1.95 – 1.68 (m, 3H). The absolute stereochemistry for the first and second eluted compounds was not determined.

Example 55: 2-(7-Chloro-1H-benzo[d]imidazole-2-carbonyl)-4-methyl-1,2,3,4-tetrahydropyrrolo[1,2-a]pyrazine-6-carbonitrile



[00323] Step A: To a solution of 4-methyl-3,4-dihydropyrrolo[1,2-a]pyrazin-1(2H)-one (800 mg, 5.33 mmol) in THF (32.0 mL) was added LAH (2.5M in THF). The mixture was degassed and purged with nitrogen three times and stirred at 70 °C for 12 h under a nitrogen atmosphere. The reaction mixture was allowed to cool to 0 °C, the reaction mixture was quenched by addition of 0.60 mL of H₂O, followed by 0.60 mL of 10% aqueous NaOH and 1.80 mL of H₂O. After being stirred at 20 °C for 5 min, then added MgSO₄, the mixture was filtered through Celite pad, then was concentrated in vacuum to give 4-methyl-1,2,3,4-tetrahydropyrrolo[1,2-a]pyrazine. LC-MS: 137.2 [M+H]⁺.

[00324] Step B: To a solution of 4-methyl-1,2,3,4-tetrahydropyrrolo[1,2-a]pyrazine (800 mg, 5.87 mmol) in DCM (10.0 mL) was added Boc₂O (1.41 g, 6.46 mmol) and TEA (594 mg, 5.87 mmol). The mixture was stirred at 20 °C for 1 h. The reaction mixture was poured into water (20.0 mL) and extracted with EtOAc (30.0 mL x 3). The combined organic layers were dried over Na₂SO₄, filtered, and concentrated under vacuum to give a residue which was purified by flash silica gel chromatography using a gradient of EtOAc/petroleum ether from 0/1 to 1/5 to

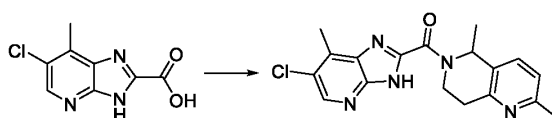
afford tert-butyl 4-methyl-3,4-dihydropyrrolo[1,2-*a*]pyrazine-2(1*H*)-carboxylate. LC-MS: 237.3 [M+H]⁺.

[00325] Step C: To a solution of tert-butyl 4-methyl-3,4-dihydropyrrolo[1,2-*a*]pyrazine-2(1*H*)-carboxylate (300 mg, 1.27 mmol) in DCM (20.0 mL) was added sulfurisocyanatidic chloride (198 mg, 1.40 mmol). The mixture was degassed and purged with nitrogen three times and stirred at 0 °C for 1 h under a nitrogen atmosphere. Then DMF (928 mg, 12.7 mmol) was added dropwise to the mixture, cooled to -10 °C. The resulting mixture was stirred at 20 °C for 5 h. The reaction mixture was poured into water (20.0 mL) and extracted with EtOAc (20.0 mL x 5). The combined organic layers were dried over Na₂SO₄, filtered, and concentrated under vacuum to give a residue which was purified by flash silica gel chromatography using a gradient of EtOAc/petroleum ether from 0/1 to 1/3 to afford tert-butyl 6-cyano-4-methyl-3,4-dihydropyrrolo[1,2-*a*]pyrazine-2(1*H*)-carboxylate. ¹H NMR (400 MHz, DMSO *d*₆) δ 6.96 (d, *J* = 4.0 Hz, 1H), 6.05 (d, *J* = 4.0 Hz, 1H), 5.06 – 4.69 (m, 1H), 4.51 – 4.11 (m, 2H), 3.54 – 3.35 (m, 1H), 1.43 (s, 9H), 1.32 (br d, *J* = 6.4 Hz, 3H).

[00326] Step D: To a solution of tert-butyl 6-cyano-4-methyl-3,4-dihydropyrrolo[1,2-*a*]pyrazine-2(1*H*)-carboxylate (180 mg, 0.689 mmol) in EtOAc (2.00 mL) was added HCl/EtOAc (4M, 10.0 mL). The resulting mixture was stirred at 20 °C for 1 h. The mixture was concentrated under vacuum at 30 °C to give 4-methyl-1,2,3,4-tetrahydropyrrolo[1,2-*a*]pyrazine-6-carbonitrile. LC-MS: 162.1 [M+H]⁺.

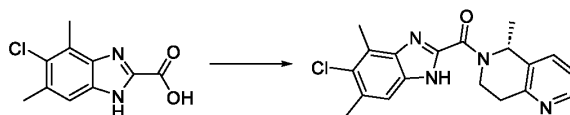
[00327] Step E: A mixture of 7-chloro-1*H*-benzo[d]imidazole-2-carboxylic acid (49.7 mg, 0.253 mmol), 4-methyl-1,2,3,4-tetrahydropyrrolo[1,2-*a*]pyrazine-6-carbonitrile (50.0 mg, 0.253 mmol), HATU (48.1 mg, 0.126 mmol) and DIEA (98.1 mg, 0.759 mmol) in DMF (1.00 mL) was stirred at 20 °C for 1 h. The reaction mixture was poured into H₂O (2.00 mL) and extracted with EtOAc (3.00 mL x 3). The combined organic layers were dried over Na₂SO₄, filtered, and concentrated under vacuum to give a residue which was purified by preparative HPLC (Phenomenex Luna C18 column (75 × 30 mm, 3 μm); flow rate: 25 mL/min; gradient: 5% – 35% B over 8 min; mobile phase A: 0.04% aqueous HCl, mobile phase B: acetonitrile) to afford 2-(7-chloro-1*H*-benzo[d]imidazole-2-carbonyl)-4-methyl-1,2,3,4-tetrahydropyrrolo[1,2-*a*]pyrazine-6-carbonitrile. LC-MS: 340.1 [M+H]⁺. ¹H NMR (400 MHz, DMSO *d*₆) δ 7.56 (br d, *J* = 8.0 Hz, 1H), 7.47 – 7.26 (m, 2H), 7.07 – 6.96 (m, 1H), 6.40 – 6.08 (m, 1H), 5.45 – 4.91 (m, 1H), 4.76 – 4.44 (m, 2H), 4.01 (br dd, *J* = 3.7, 13.9 Hz, 2H), 1.42 (dd, *J* = 3.8, 6.3 Hz, 3H).

Example 56: (6-Chloro-7-methyl-3*H*-imidazo[4,5-*b*]pyridin-2-yl)(2,5-dimethyl-7,8-dihydro-1,6-naphthyridin-6(5*H*)-yl)methanone



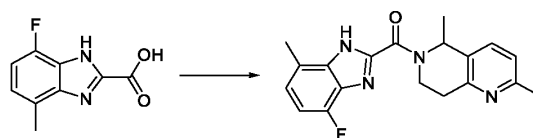
[00328] The title compound was prepared from 2,5-dimethyl-5,6,7,8-tetrahydro-1,6-naphthyridine and 6-chloro-7-methyl-3H-imidazo[4,5-b]pyridine-2-carboxylic acid according to the procedure of Example 1, Step A. LC-MS: 356.1 $[M+H]^+$. 1H NMR (400 MHz, DMSO- d_6) δ 8.55 – 8.30 (m, 2H), 7.85 – 7.66 (m, 1H), 6.58 – 5.79 (m, 1H), 5.53 – 4.68 (m, 1H), 3.53 – 3.06 (m, 3H), 2.76 – 2.68 (m, 3H), 2.67 – 2.61 (m, 3H), 1.75 (d, J = 6.8 Hz, 1H), 1.59 (d, J = 6.8 Hz, 2H).

Example 57: (R)-(5-Chloro-4,6-dimethyl-1H-benzo[d]imidazol-2-yl)(5-methyl-7,8-dihydro-1,6-naphthyridin-6(5H)-yl)methanone



[00329] The title compound was prepared from (R)-5-methyl-5,6,7,8-tetrahydro-1,6-naphthyridine and 5-chloro-4,6-dimethyl-1H-benzimidazole-2-carboxylic acid according to the procedure of Example 1, Step A. LC-MS: 355.1 $[M+H]^+$. 1H NMR (400 MHz, $CDCl_3$) δ 8.60 (br d, J = 3.4 Hz, 1H), 8.31 – 8.07 (m, 1H), 7.88 – 7.69 (m, 1H), 7.40 (br d, J = 15.4 Hz, 1H), 6.04 (br d, J = 7.3 Hz, 1H), 5.19 – 3.19 (m, 4H), 2.71 – 2.50 (m, 6H), 1.85 (br d, J = 6.6 Hz, 1H), 1.70 (br d, J = 6.9 Hz, 2H).

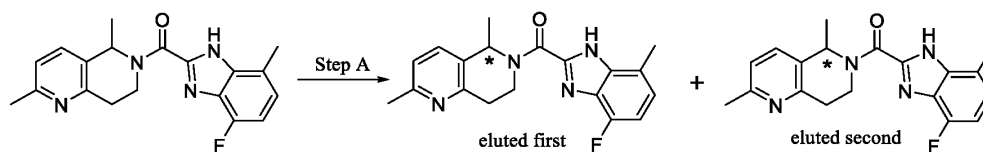
Example 58: (2,5-Dimethyl-7,8-dihydro-1,6-naphthyridin-6(5H)-yl)(4-fluoro-7-methyl-1H-benzo[d]imidazol-2-yl)methanone



[00330] The title compound was prepared from 2,5-dimethyl-5,6,7,8-tetrahydro-1,6-naphthyridine and 7-fluoro-4-methyl-1H-benzo[d]imidazole-2-carboxylic acid according to the procedure of Example 1, Step A. LC-MS: 339.1 $[M+H]^+$. 1H NMR (400 MHz, DMSO- d_6) δ 8.54 – 8.33 (m, 1H), 7.88 – 7.67 (m, 1H), 7.13 – 6.91 (m, 2H), 6.61 – 5.82 (m, 1H), 5.62 – 4.72 (m, 1H), 4.93 – 4.63 (m, 1H), 3.98 – 3.54 (m, 2H), 3.48 – 2.99 (m, 3H), 2.71 (br s, 3H), 1.84 – 1.51 (m, 3H).

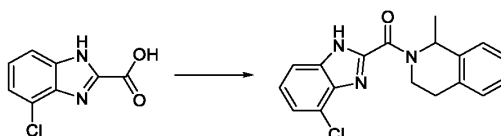
Examples 58A and 58B: (R) or (S)-(2,5-Dimethyl-7,8-dihydro-1,6-naphthyridin-6(5H)-yl)(4-fluoro-7-methyl-1H-benzo[d]imidazol-2-yl)methanone and (R) or (S)-(2,5-Dimethyl-

7,8-dihydro-1,6-naphthyridin-6(5H)-yl)(4-fluoro-7-methyl-1H-benzo[d]imidazol-2-yl)methanone



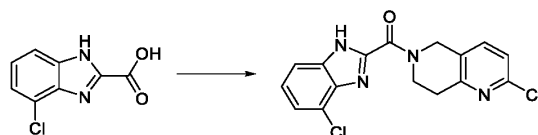
[00331] Step A: (2,5-Dimethyl-7,8-dihydro-1,6-naphthyridin-6(5H)-yl)(4-fluoro-7-methyl-1H-benzo[d]imidazol-2-yl)methanone (20.0 mg, 0.059 mmol) was separated by SFC separation (ChiralPak IH (250 × 30 mm, 10 μm); flow rate: 30 mL/min; gradient: 50% B over 14 min; mobile phase A: heptane, mobile phase B: CO₂ - EtOH(0.1% NH₃H₂O) to afford a first eluted compound and a second eluted compound. First eluted compound (**Example 58A**): LC-MS: 339.1 [M+H]⁺. ¹H NMR (400 MHz, CDCl₃) δ 10.71 – 10.27 (m, 1H), 7.87 – 7.59 (m, 1H), 7.22 – 6.85 (m, 3H), 6.58 – 4.94 (m, 2H), 3.74 – 3.32 (m, 3H), 2.76 – 2.50 (m, 6H), 1.80 (br s, 1H), 1.63 (br d, J = 6.6 Hz, 2H). Second eluted compound (**Example 58B**): LC-MS: 339.1 [M+H]⁺. ¹H NMR (400 MHz, CDCl₃) δ 10.86 – 10.50 (m, 1H), 7.61 – 7.40 (m, 1H), 7.22 – 6.88 (m, 3H), 6.49 – 4.93 (m, 2H), 3.87 – 3.11 (m, 3H), 2.74 – 2.45 (m, 6H), 1.77 (br d, J = 6.6 Hz, 2H), 1.61 (br d, J = 6.6 Hz, 1H). The absolute stereochemistry for the first and second eluted compounds was not determined.

Example 59: (4-Chloro-1H-benzo[d]imidazol-2-yl)(1-methyl-3,4-dihydroisoquinolin-2(1H)-yl)methanone



[00332] The title compound was prepared from 1-methyl-1,2,3,4-tetrahydroisoquinoline and 4-chloro-1H-benzo[d]imidazole-2-carboxylic acid according to the procedure of Example 1, Step A. LC-MS: 326.1 [M+H]⁺.

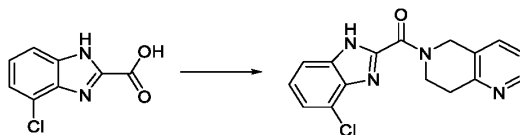
Example 60: (4-Chloro-1H-benzo[d]imidazol-2-yl)(2-chloro-7,8-dihydro-1,6-naphthyridin-6(5H)-yl)methanone



[00333] The title compound was prepared from 2-chloro-5,6,7,8-tetrahydro-1,6-naphthyridine and 4-chloro-1H-benzo[d]imidazole-2-carboxylic acid according to the procedure of Example 1, Step A. LC-MS: 347.2 [M+H]⁺. ¹H NMR (400 MHz, CDCl₃) δ 7.89 – 7.69 (m, 1H), 7.58 – 7.44

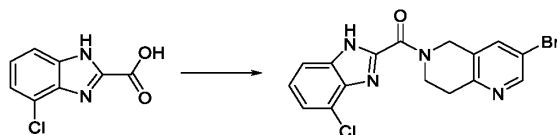
(m, 1H), 7.40 – 7.36 (m, 1H), 7.31 (br d, $J = 6.9$ Hz, 1H), 7.23 (dd, $J = 4.7, 8.0$ Hz, 1H), 6.05 – 5.73 (m, 1H), 5.11 – 4.88 (m, 2H), 4.18 (t, $J = 6.2$ Hz, 1H), 3.34 – 3.01 (m, 2H).

Example 61: (4-Chloro-1H-benzo[d]imidazol-2-yl)(7,8-dihydro-1,6-naphthyridin-6(5H)-yl)methanone



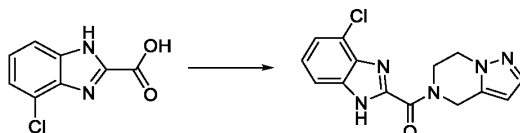
[00334] The title compound was prepared from 5,6,7,8-tetrahydro-1,6-naphthyridine and 4-chloro-1H-benzo[d]imidazole-2-carboxylic acid according to the procedure of Example 1, Step A. LC-MS: 313.3 $[M+H]^+$.

Example 62: (3-Bromo-7,8-dihydro-1,6-naphthyridin-6(5H)-yl)(4-chloro-1H-benzo[d]imidazol-2-yl)methanone



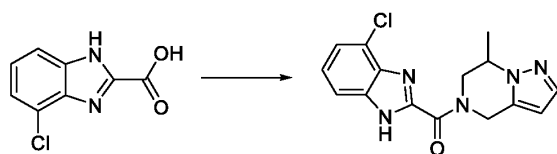
[00335] The title compound was prepared from 3-bromo-5,6,7,8-tetrahydro-1,6-naphthyridine and 4-chloro-1H-benzo[d]imidazole-2-carboxylic acid according to the procedure of Example 1, Step A. LC-MS: 393.2 $[M+H]^+$.

Example 63: (4-Chloro-1H-benzo[d]imidazol-2-yl)(6,7-dihydropyrazolo[1,5-a]pyrazin-5(4H)-yl)methanone



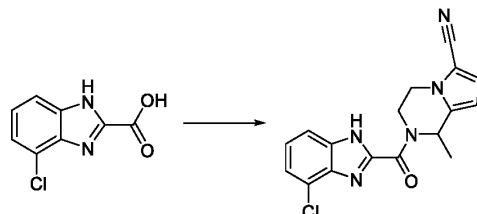
[00336] The title compound was prepared from 4,5,6,7-tetrahydropyrazolo[1,5-a]pyrazine and 4-chloro-1H-benzo[d]imidazole-2-carboxylic acid according to the procedure of Example 1, Step A. LC-MS: 302.1 $[M+H]^+$.

Example 64: (4-Chloro-1H-benzo[d]imidazol-2-yl)(7-methyl-6,7-dihydropyrazolo[1,5-a]pyrazin-5(4H)-yl)methanone



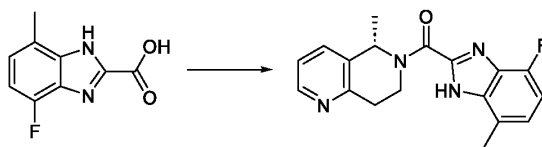
[00337] The title compound was prepared from (S)-7-methyl-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrazine and 4-chloro-1H-benzo[d]imidazole-2-carboxylic acid according to the procedure of Example 1, Step A. LC-MS: 316.1 [M+H]⁺.

Example 65: 2-(4-Chloro-1H-benzo[d]imidazole-2-carbonyl)-1-methyl-1,2,3,4-tetrahydropyrrolo[1,2-a]pyrazine-6-carbonitrile



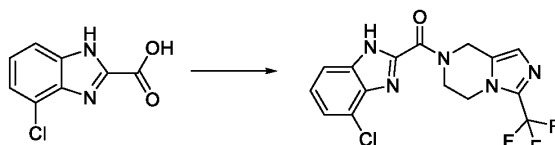
[00338] The title compound was prepared from 1-methyl-1,2,3,4-tetrahydropyrrolo[1,2-a]pyrazine-6-carbonitrile and 4-chloro-1H-benzo[d]imidazole-2-carboxylic acid according to the procedure of Example 1, Step A. LC-MS: 340.1 [M+H]⁺.

Example 66: (S)-(4-Fluoro-7-methyl-1H-benzo[d]imidazol-2-yl)(5-methyl-7,8-dihydro-1,6-naphthyridin-6(5H)-yl)methanone



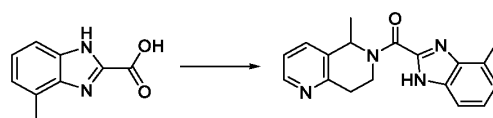
[00339] The title compound was prepared from (S)-5-methyl-5,6,7,8-tetrahydro-1,6-naphthyridine and 4-fluoro-7-methyl-1H-benzo[d]imidazole-2-carboxylic acid according to the procedure of Example 1, Step A. LC-MS: 325.1 [M+H]⁺. ¹H NMR (400 MHz, DMSO-*d*₆) δ 8.83 – 8.43 (m, 2H), 8.00 – 7.72 (m, 1H), 7.21 – 6.88 (m, 2H), 6.64 – 5.84 (m, 1H), 5.63 – 4.74 (m, 3H), 3.79 – 3.14 (m, 4H), 1.81 – 1.60 (m, 3H).

Example 67: 4-Chloro-1H-benzo[d]imidazol-2-yl(3-(trifluoromethyl)-5,6-dihydroimidazo[1,5-a]pyrazin-7(8H)-yl)methanone



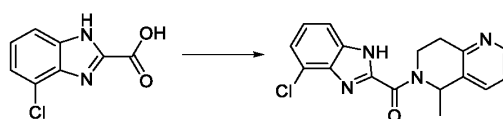
[00340] The title compound was prepared from 3-(trifluoromethyl)-5,6,7,8-tetrahydroimidazo[1,5-a]pyrazine and 4-chloro-1H-benzo[d]imidazole-2-carboxylic acid according to the procedure of Example 1, Step A. LC-MS: 370.0 [M+H]⁺.

Example 68: (4-Methyl-1H-benzimidazol-2-yl)-(5-methyl-7,8-dihydro-5H-1,6-naphthyridin-6-yl)methanone



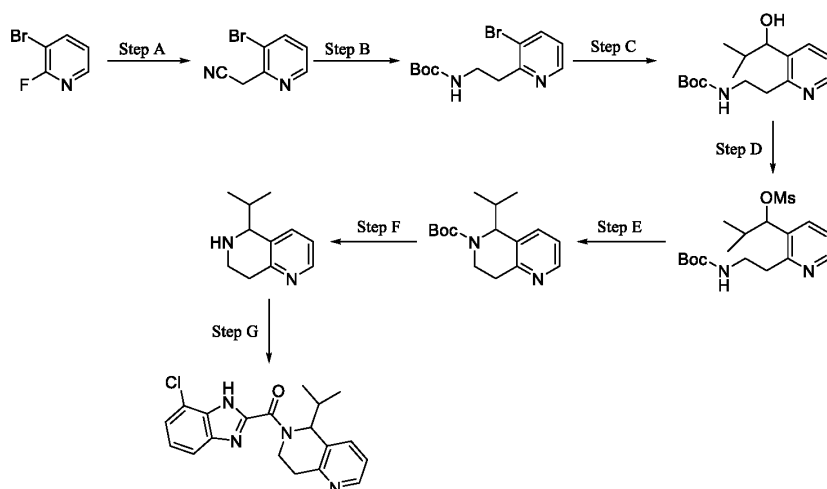
[00341] The title compound was prepared from 5-methyl-5,6,7,8-tetrahydro-1,6-naphthyridine and 4-methyl-1H-benzo[d]imidazole-2-carboxylic acid according to the procedure of Example 1, Step A. LC-MS: 306.9 $[M+H]^+$. 1H NMR (400 MHz, $CDCl_3$) δ 8.49 (br d, $J = 4.6$ Hz, 1H), 7.77 – 7.52 (m, 1H), 7.42 – 7.29 (m, 1H), 7.26 – 7.07 (m, 2H), 6.71 – 6.31 (m, 1H), 6.01 – 4.85 (m, 1H), 3.98 – 3.06 (m, 1H), 3.53 – 3.05 (m, 1H), 2.79 – 2.38 (m, 3H), 1.92 – 1.52 (m, 4H).

Example 69: (4-Chloro-1H-benzo[d]imidazol-2-yl)(5-methyl-7,8-dihydro-1,6-naphthyridin-6(5H)-yl)methanone



[00342] The title compound was prepared from 5-methyl-5,6,7,8-tetrahydro-1,6-naphthyridine and 4-chloro-1H-benzo[d]imidazole-2-carboxylic acid according to the procedure of Example 1, Step A. LC-MS: 336.2 $[M+H]^+$.

Example 70: (7-Chloro-1H-benzo[d]imidazol-2-yl)(5-isopropyl-7,8-dihydro-1,6-naphthyridin-6(5H)-yl)methanone



[00343] Step A: To a solution of LiHMDS (56.8 mL, 56.8 mmol, 1M) in THF (30.0 mL) was added dropwise acetonitrile (2.34 g, 56.8 mmol) at $-78^\circ C$ under nitrogen, and the mixture was stirred at $-78^\circ C$ for 1 h. Then 3-bromo-2-fluoropyridine (5.00 g, 28.4 mmol) in THF (30.0 mL) was added dropwise at $-78^\circ C$. The mixture was stirred at same temperature for 2 h then stirred at $20^\circ C$ for 12 h under nitrogen. The reaction mixture was poured into H_2O (80.0 mL) and washed with EtOAc (100 mL x 3). The combined organic layers were dried over Na_2SO_4 ,

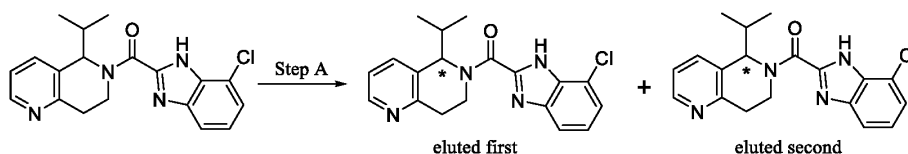
filtered, and concentrated under vacuum to give a residue which was purified by flash silica gel chromatography using a gradient of EtOAc/petroleum ether from 0/1 to 1/5 to afford 2-(3-bromopyridin-2-yl)acetonitrile. LC-MS: 197.1 $[M+H]^+$.

[00344] Step B: To a solution of Raney Ni (4.20 g, 49.0 mmol) in MeOH (420 mL) was added 2-(3-bromopyridin-2-yl)acetonitrile (4.20 g, 21.3 mmol) and Boc_2O (23.3 g, 107 mmol). The mixture was stirred at 20 °C for 2 h under hydrogen. The mixture was filtered through Celite pad, filtered, and concentrated under vacuum to give a residue which was purified by flash silica gel chromatography using a gradient of EtOAc/petroleum ether from 0/1 to 1/5 to afford tert-butyl (2-(3-bromopyridin-2-yl)ethyl)carbamate. LC-MS: 301.1 $[M+H]^+$.

[00345] Step C: To a solution of tert-butyl (2-(3-bromopyridin-2-yl)ethyl)carbamate (2.25 g, 7.47 mmol) in THF (40.0 mL) was added n-BuLi (5.98 mL, 14.9 mmol, 2.5M) at – 78 °C for 1 h under nitrogen. Then isobutyraldehyde (5.39 g, 74.7 mmol) in THF (40.0 mL) was added at – 78 °C. The mixture was stirred at 20 °C for 12 h. The reaction mixture was poured into H_2O (100 mL) and washed with EtOAc (100 mL x 3). The combined organic layers were dried over Na_2SO_4 , filtered, and concentrated under vacuum to give a residue which was purified by flash silica gel chromatography using a gradient of EtOAc/petroleum ether from 0/1 to 1/3 to afford tert-butyl (2-(3-(1-hydroxy-2-methylpropyl)pyridin-2-yl)ethyl)carbamate. LC-MS: 295.3 $[M+H]^+$.

[00346] Steps D, E, F, and G: (7-Chloro-1H-benzo[d]imidazol-2-yl)(5-isopropyl-7,8-dihydro-1,6-naphthyridin-6(5H)-yl)methanone was prepared from tert-butyl (2-(3-(1-hydroxy-2-methylpropyl)pyridin-2-yl)ethyl)carbamate according to the procedure of Example 11, Steps E, F, G, and H. LC-MS: 355.0 $[M+H]^+$. ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ 8.87 – 8.66 (m, 1H), 8.60 – 8.19 (m, 1H), 7.96 – 7.78 (m, 1H), 7.58 – 7.49 (m, 1H), 7.40 – 7.29 (m, 2H), 5.64 (br d, $J = 9.4$ Hz, 1H), 3.90 – 3.23 (m, 4H), 2.37 – 2.21 (m, 1H), 1.17 – 0.95 (m, 6H).

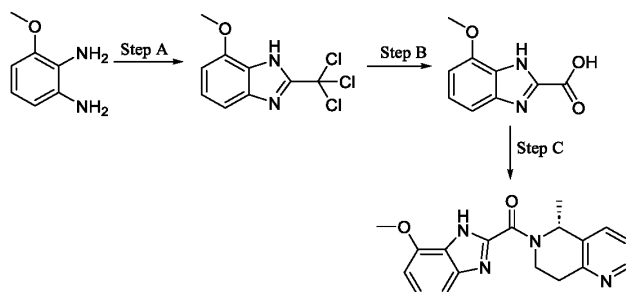
Examples 70A and 70B: (R) or (S)-(7-Chloro-1H-benzo[d]imidazol-2-yl)(5-isopropyl-7,8-dihydro-1,6-naphthyridin-6(5H)-yl)methanone and (R) or (S)-(7-Chloro-1H-benzo[d]imidazol-2-yl)(5-isopropyl-7,8-dihydro-1,6-naphthyridin-6(5H)-yl)methanone



[00347] Step A: (7-Chloro-1H-benzo[d]imidazol-2-yl)(5-isopropyl-7,8-dihydro-1,6-naphthyridin-6(5H)-yl)methanone (10.0 mg, 0.028 mmol) was separated by SFC separation ((Phenomenex-Cellulose-2 (250 × 30 mm, 10 μm); flow rate: 70 mL/min; gradient: 33 – 33% B

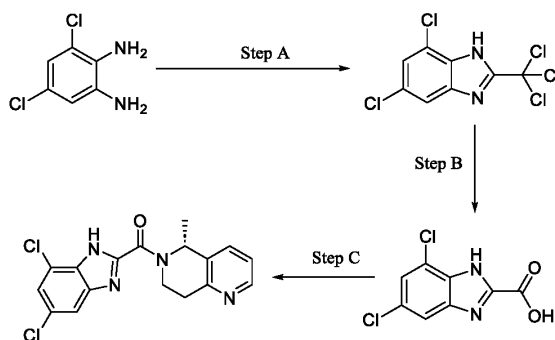
over 11 min; mobile phase A: CO₂, mobile phase B: EtOH (0.1% NH₃H₂O)) to afford a first eluted compound and a second eluted compound. First eluted compound (**Example 70A**): LC-MS: 355.1 [M+H]⁺. ¹H NMR (400 MHz, DMSO-*d*₆) δ 8.50 – 8.35 (m, 1H), 7.72 (d, *J* = 7.6 Hz, 1H), 7.57 – 7.48 (m, 1H), 7.40 – 7.20 (m, 3H), 5.60 – 5.31 (m, 1H), 3.96 – 3.49 (m, 1H), 3.20 – 2.92 (m, 3H), 2.31 – 2.17 (m, 1H), 1.08 – 0.97 (m, 6H). Second eluted compound (**Example 70B**): LC-MS: 355.1 [M+H]⁺. ¹H NMR (400 MHz, DMSO-*d*₆) δ 8.65 – 8.27 (m, 1H), 7.84 – 7.66 (m, 1H), 7.60 – 7.44 (m, 1H), 7.37 – 7.19 (m, 3H), 5.41 (d, *J* = 9.1 Hz, 1H), 4.04 – 3.68 (m, 1H), 3.18 – 2.99 (m, 3H), 2.28 – 2.11 (m, 1H), 1.08 – 0.97 (m, 6H). The absolute stereochemistry for the first and second eluted compounds was not determined.

Example 71: (R)-(7-Methoxy-1H-benzo[d]imidazol-2-yl)(5-methyl-7,8-dihydro-1,6-naphthyridin-6(5H)-yl)methanone



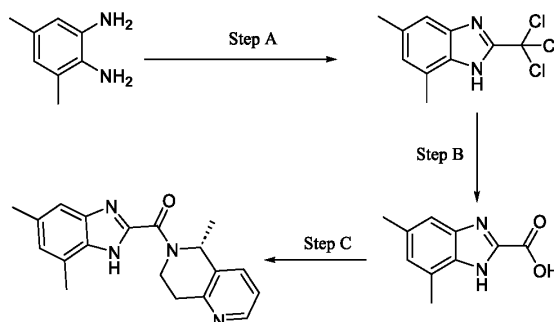
[00348] (R)-(7-Methoxy-1H-benzo[d]imidazol-2-yl)(5-methyl-7,8-dihydro-1,6-naphthyridin-6(5H)-yl)methanone was prepared from 3-methoxybenzene-1,2-diamine according to the procedure of Example 30, Steps A, B, and C. LC-MS: 323.1 [M+H]⁺. ¹H NMR (400 MHz, DMSO-*d*₆) δ 13.24 – 12.87 (m, 1H), 8.55 – 8.27 (m, 1H), 7.89 – 7.54 (m, 1H), 7.41 – 6.97 (m, 3H), 6.83 – 6.63 (m, 1H), 5.90 – 5.60 (m, 1H), 3.96 (s, 3H), 3.75 – 3.62 (m, 2H), 3.04 – 2.88 (m, 2H), 1.72 – 1.47 (m, 3H).

Example 72: (R)-(5,7-Dichloro-1H-benzo[d]imidazol-2-yl)(5-methyl-7,8-dihydro-1,6-naphthyridin-6(5H)-yl)methanone



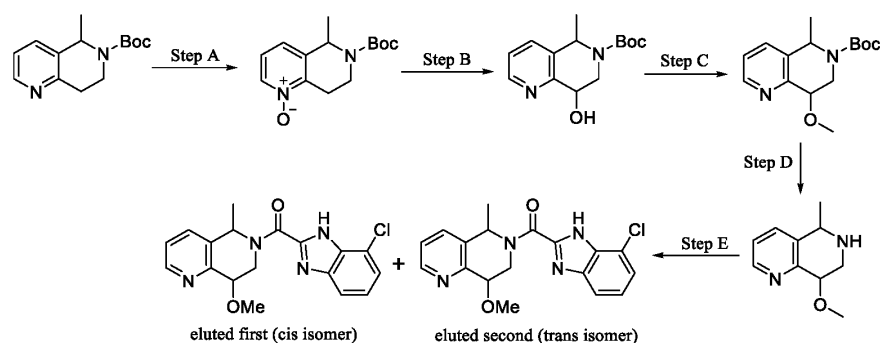
[00349] (R)-(5,7-Dichloro-1H-benzo[d]imidazol-2-yl)(5-methyl-7,8-dihydro-1,6-naphthyridin-6(5H)-yl)methanone was prepared from 3,5-dichlorobenzene-1,2-diamine according to the procedure of Example 30, Steps A, B, and C. LC-MS: 361.1 [M+H]⁺. ¹H NMR (400 MHz, MeOD) δ 8.76 – 8.52 (m, 2H), 8.03 – 7.88 (m, 1H), 7.67 – 7.35 (m, 2H), 7.09 – 5.98 (m, 1H), 5.97 – 4.94 (m, 1H), 3.85 – 3.32 (m, 3H), 1.94 – 1.68 (m, 3H).

Example 73: (R)-(5,7-Dimethyl-1H-benzo[d]imidazol-2-yl)(5-methyl-7,8-dihydro-1,6-naphthyridin-6(5H)-yl)methanone



[00350] (R)-(5,7-Dimethyl-1H-benzo[d]imidazol-2-yl)(5-methyl-7,8-dihydro-1,6-naphthyridin-6(5H)-yl)methanone was prepared from 3,5-dimethylbenzene-1,2-diamine according to the procedure of Example 30, Steps A, B, and C. LC-MS: 321.2 [M+H]⁺. ¹H NMR (400 MHz, MeOD) δ 8.75 (d, *J* = 5.8 Hz, 1H), 8.68 – 8.37 (m, 1H), 7.99 (br s, 1H), 7.51 – 7.18 (m, 2H), 6.04 (q, *J* = 6.8 Hz, 1H), 4.72 – 4.52 (m, 1H), 4.01 – 3.44 (m, 2H), 3.29 – 3.12 (m, 1H), 2.72 – 2.35 (m, 6H), 1.77 (d, *J* = 6.9 Hz, 3H).

Examples 74A and 74B: rac-(7-Chloro-1H-benzo[d]imidazol-2-yl)((cis)-8-methoxy-5-methyl-7,8-dihydro-1,6-naphthyridin-6(5H)-yl)methanone and rac-(7-Chloro-1H-benzo[d]imidazol-2-yl)((trans)-8-methoxy-5-methyl-7,8-dihydro-1,6-naphthyridin-6(5H)-yl)methanone



[00351] Step A: To a solution of tert-butyl 5-methyl-7,8-dihydro-1,6-naphthyridine-6(5H)-carboxylate (5.00 g, 20.0 mmol) in DCM (50.0 mL) was added m-CPBA (8.00 g, 40.0 mmol,

85% purity). The mixture was stirred at 25 °C for 2 h. The residue was diluted with sat.aq Na₂SO₃ (200 mL) and extracted with DCM (200 mL x 3). The combined organic layers were dried over Na₂SO₄, filtered and concentrated to give 6-(tert-butoxycarbonyl)-5-methyl-5,6,7,8-tetrahydro-1,6-naphthyridine 1-oxide. LC-MS: 265.2 [M+H]⁺.

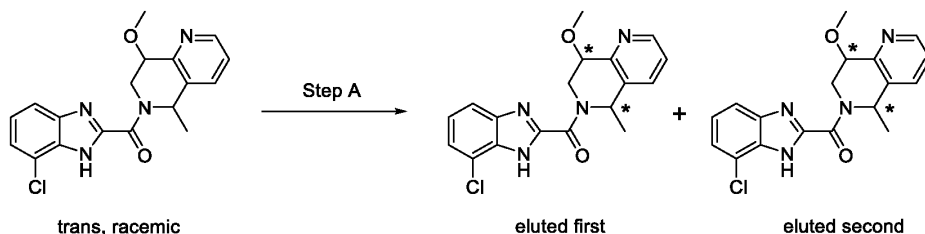
[00352] Step B: To a solution of 6-(tert-butoxycarbonyl)-5-methyl-5,6,7,8-tetrahydro-1,6-naphthyridine 1-oxide (4.00 g, 15.0 mmol) in DMF (40.0 mL) was added TFAA (13.0 g, 61.0 mmol) at 0 °C. The mixture was stirred at 60 °C for 1 h. The reaction mixture was concentrated under reduced pressure to remove solvent. The residue was diluted with Na₂CO₃ (60.0 mL) and extracted with EtOAc (80.0 mL x 3). The combined organic layers were washed with sat.aq LiCl (80.0 mL x 5), dried over Na₂SO₄, filtered and concentrated to give a residue which was purified by flash silica gel chromatography using a gradient of Dichloromethane/Methanol from 95/5 to 91/9 to afford tert-butyl 8-hydroxy-5-methyl-7,8-dihydro-1,6-naphthyridine-6(5H)-carboxylate. LC-MS: 265.2 [M+H]⁺.

[00353] Step C: To a solution of tert-butyl 8-hydroxy-5-methyl-7,8-dihydro-1,6-naphthyridine-6(5H)-carboxylate (500 mg, 2.00 mmol) in THF (5.00 mL) was added t-BuONa (545 mg, 6.00 mmol) and MeI (537 mg, 4.00 mmol). The mixture was stirred at 25 °C for 2 h under Nitrogen atmosphere. The reaction mixture was concentrated under reduced pressure to remove solvent. The residue was diluted with H₂O (20.0 mL) and extracted with EtOAc (30.0 mL x 3). The combined organic layers were washed with sat. aqueous LiCl (10.0 mL x 5), dried over Na₂SO₄, filtered to give tert-butyl 8-methoxy-5-methyl-7,8-dihydro-1,6-naphthyridine-6(5H)-carboxylate. LC-MS: 279.2 [M+H]⁺.

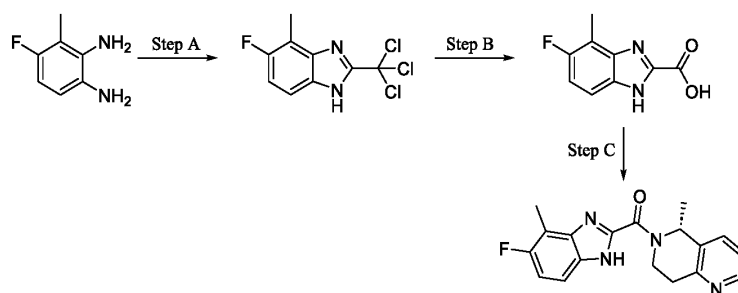
[00354] Step D: To a solution of tert-butyl 8-methoxy-5-methyl-7,8-dihydro-1,6-naphthyridine-6(5H)-carboxylate (200 mg, 0.719 mmol) in 4M HCl/EtOAc (5.00 mL). The mixture was stirred at 25 °C for 1 h. The reaction mixture was concentrated under reduced pressure to give 8-methoxy-5-methyl-5,6,7,8-tetrahydro-1,6-naphthyridine. LC-MS: 179.3 [M+H]⁺.

[00355] Step E: To a solution of 8-methoxy-5-methyl-5,6,7,8-tetrahydro-1,6-naphthyridine (68.0 mg, 0.382 mmol) and 7-chloro-1H-benzo[d]imidazole-2-carboxylic acid (50.0 mg, 0.254 mmol) in DMF (1.00 mL) was added DIEA (99.0 mg, 0.764 mmol) and HATU (49.0 mg, 0.127 mmol). The mixture was stirred at 25 °C for 12 h. The reaction mixture was concentrated under reduced pressure to give a residue which was purified by preparative HPLC (column: Phenomenex luna C18 100 x 40mm x 5 µm; mobile phase: [H₂O (0.04% HCl) -ACN]; gradient: 15%-35% B over 8.0 min) to afford (7-chloro-1H-benzo[d]imidazol-2-yl)((cis)-8-methoxy-5-methyl-7,8-dihydro-1,6-naphthyridin-6(5H)-yl)methanone (**Example 74A**) (eluted first, cis isomer) and (7-chloro-1H-benzo[d]imidazol-2-yl)((cis)-8-methoxy-5-methyl-7,8-dihydro-1,6-

Examples 74C and 74D: (5R,8S) or (5S,8R)-(7-Chloro-1H-benzo[d]imidazol-2-yl)(8-methoxy-5-methyl-7,8-dihydro-1,6-naphthyridin-6(5H)-yl)methanone and (5R,8S) or (5S,8R)-(7-Chloro-1H-benzo[d]imidazol-2-yl)(8-methoxy-5-methyl-7,8-dihydro-1,6-naphthyridin-6(5H)-yl)methanone

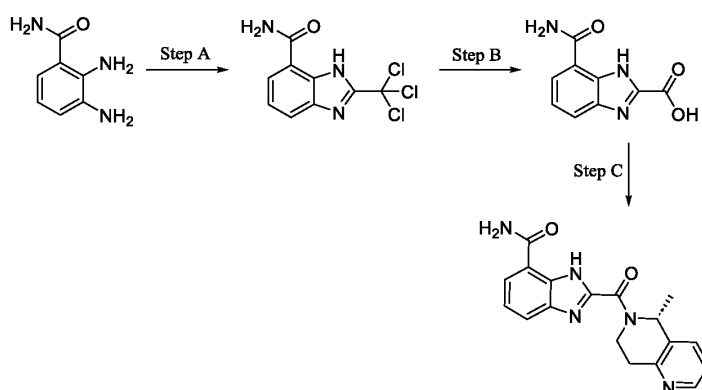


Example 75: (R)-(5-Fluoro-4-methyl-1H-benzo[d]imidazol-2-yl)(5-methyl-7,8-dihydro-1,6-naphthyridin-6(5H)-yl)methanone



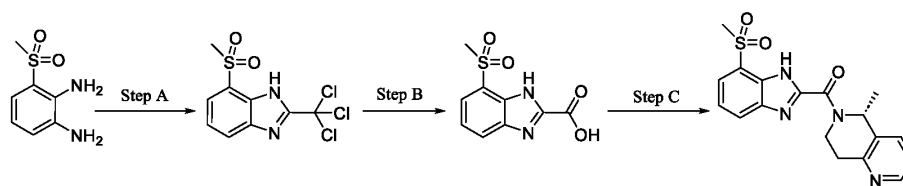
[00357] (R)-(5-Fluoro-4-methyl-1H-benzo[d]imidazol-2-yl)(5-methyl-7,8-dihydro-1,6-naphthyridin-6(5H)-yl)methanone was prepared from 4-fluoro-3-methylbenzene-1,2-diamine according to the procedure of Example 30, Steps A, B, and C. LC-MS: 325.1 [M+H]⁺. ¹H NMR (400 MHz, DMSO-*d*₆) δ 8.79 – 8.71 (m, 1H), 8.58 – 8.42 (m, 1H), 8.00 – 7.69 (m, 1H), 7.48 (br d, *J* = 3.3 Hz, 1H), 7.19 – 7.12 (m, 1H), 6.93 – 6.64 (m, 1H), 6.05 – 5.72 (m, 2H), 4.80 (br dd, *J* = 4.8, 13.8 Hz, 1H), 3.78 – 3.61 (m, 1H), 3.54 – 3.12 (m, 3H), 1.78 (d, *J* = 6.8 Hz, 1H), 1.61 (d, *J* = 6.8 Hz, 2H).

Example 76: (R)-2-(5-Methyl-5,6,7,8-tetrahydro-1,6-naphthyridine-6-carbonyl)-1H-benzo[d]imidazole-7-carboxamide



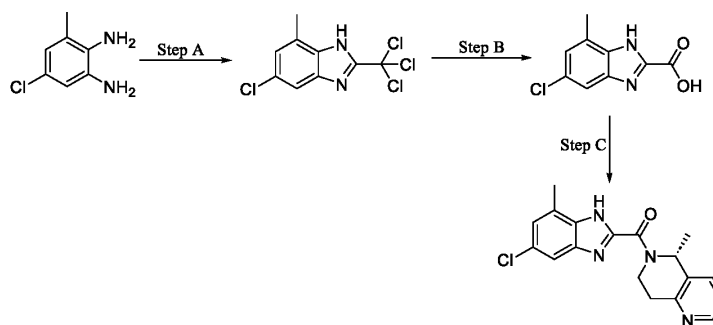
[00358] (R)-2-(5-Methyl-5,6,7,8-tetrahydro-1,6-naphthyridine-6-carbonyl)-1H-benzo[d]imidazole-7-carboxamide was prepared from 2,3-diaminobenzamide according to the procedure of Example 30, Steps A, B, and C. LC-MS: 336.1 [M+H]⁺. ¹H NMR (400 MHz, CDCl₃) δ 10.97 – 10.70 (m, 1H), 9.38 – 8.97 (m, 1H), 8.50 (br t, *J* = 3.7 Hz, 1H), 8.32 – 8.02 (m, 1H), 7.75 (d, *J* = 8.1 Hz, 1H), 7.63 – 7.34 (m, 2H), 7.25 – 7.18 (m, 1H), 6.10 – 5.80 (m, 2H), 4.08 – 3.00 (m, 3H), 1.89 – 1.67 (m, 3H).

Example 77: (R)-(5-Methyl-7,8-dihydro-1,6-naphthyridin-6(5H)-yl)(7-(methylsulfonyl)-1H-benzo[d]imidazol-2-yl)methanone



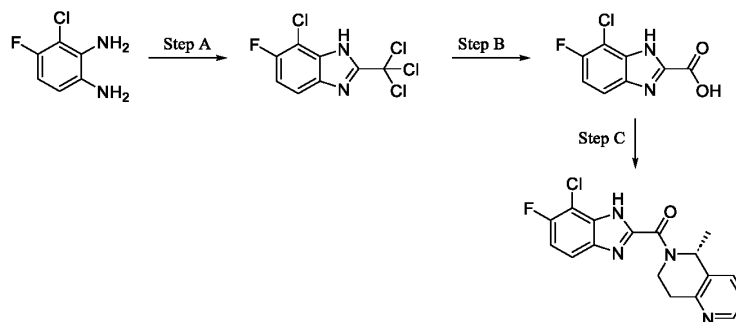
[00359] *(R)*-(5-Methyl-7,8-dihydro-1,6-naphthyridin-6(5*H*)-yl)(7-(methylsulfonyl)-1*H*-benzo[d]imidazol-2-yl)methanone was prepared from 3-methylsulfonylbenzene-1,2-diamine according to the procedure of Example 30, Steps A, B, and C. LC-MS: 371.1 [M+H]⁺. ¹H NMR (400 MHz, DMSO-*d*₆) δ 8.92 – 8.34 (m, 2H), 8.06 – 7.79 (m, 3H), 7.64 – 7.49 (m, 1H), 6.81 – 5.78 (m, 1H), 5.64 – 4.64 (m, 1H), 3.81 – 3.71 (m, 1H), 3.55 – 3.51 (m, 3H), 3.43 – 3.16 (m, 2H), 1.86 – 1.57 (m, 3H).

Example 78: (R)-(5-Chloro-7-methyl-1*H*-benzo[d]imidazol-2-yl)(5-methyl-7,8-dihydro-1,6-naphthyridin-6(5*H*)-yl)methanone



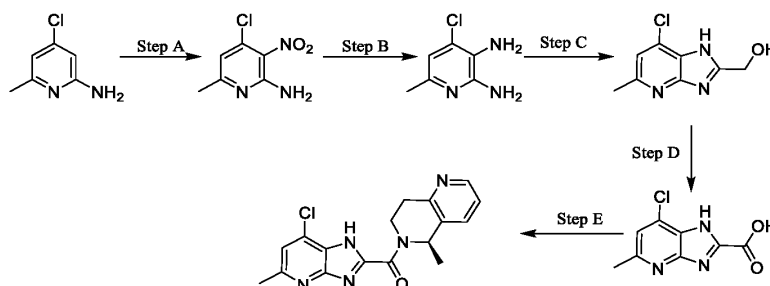
[00360] *(R)*-(5-Chloro-7-methyl-1*H*-benzo[d]imidazol-2-yl)(5-methyl-7,8-dihydro-1,6-naphthyridin-6(5*H*)-yl)methanone was prepared from 5-chloro-3-methylbenzene-1,2-diamine according to the procedure of Example 30, Steps A, B, and C. LC-MS: 341.2 [M+H]⁺. ¹H NMR (400 MHz, DMSO-*d*₆) δ 8.85 – 8.48 (m, 2H), 8.00 – 7.80 (m, 1H), 7.60 – 6.65 (m, 3H), 6.03 – 5.55 (m, 2H), 4.91 – 3.61 (m, 1H), 3.54 – 3.06 (m, 2H), 2.58 (s, 3H), 1.77 (d, *J* = 6.8 Hz, 1H), 1.61 (d, *J* = 6.9 Hz, 2H).

Example 79: (R)-(7-Chloro-6-fluoro-1*H*-benzo[d]imidazol-2-yl)(5-methyl-7,8-dihydro-1,6-naphthyridin-6(5*H*)-yl)methanone



[00361] (R)-(7-Chloro-6-fluoro-1H-benzo[d]imidazol-2-yl)(5-methyl-7,8-dihydro-1,6-naphthyridin-6(5H)-yl)methanone was prepared from 3-chloro-4-fluorobenzene-1,2-diamine according to the procedure of Example 30, Steps A, B, and C. LC-MS: 345.1 [M+H]⁺. ¹H NMR (400 MHz, CDCl₃) δ 10.90 – 10.58 (m, 1H), 8.51 – 8.42 (m, 1H), 7.75 – 7.36 (m, 2H), 7.26 – 7.15 (m, 2H), 7.14 – 6.21 (m, 1H), 5.95 – 4.90 (m, 1H), 3.11 (br s, 3H), 1.84 – 1.75 (m, 1H), 1.64 (d, *J* = 6.9 Hz, 2H).

Example 80: (R)-(7-Chloro-5-methyl-1H-imidazo[4,5-*b*]pyridin-2-yl)(5-methyl-7,8-dihydro-1,6-naphthyridin-6(5H)-yl)methanone



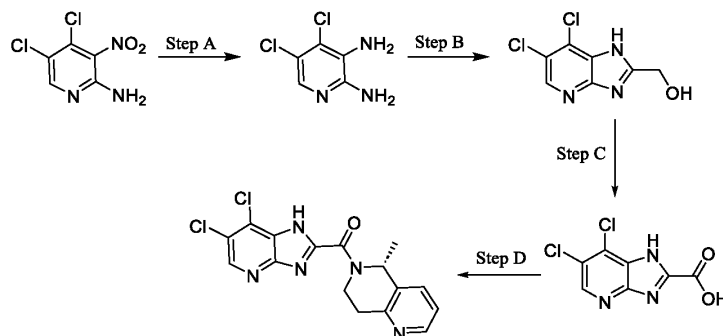
[00362] Step A: To a solution of 4-chloro-6-methylpyridin-2-amine (4.50 g, 31.6 mmol) in H₂SO₄ (45.0 mL) was added HNO₃ (3.07 g, 33.1 mmol, 2.2 mL) drop wise at 0 °C. The mixture was stirred at 20 °C for 12 h. The reaction mixture was diluted with H₂O (50.0 mL) and adjusted to pH 7 with KOH solid. The mixture was filtered and the filter cake was dried under vacuum to give a crude product, which was purified by flash silica gel chromatography using a gradient of EtOAc/petroleum ether from 1/100 to 2/5 to afford 4-chloro-6-methyl-3-nitropyridin-2-amine. LC-MS: 188.1 [M+H]⁺.

[00363] Step B: To a solution of 4-chloro-6-methyl-3-nitropyridin-2-amine (1.70 g, 9.06 mmol) in i-PrOH (30.0 mL) and H₂O (10.0 mL) was added Fe (2.53 g, 45.3 mmol) and NH₄Cl (2.42 g, 45.3 mmol). The mixture was stirred at 70 °C for 2 h. The reaction mixture was concentrated under vacuum to give a residue, which was purified by flash silica gel chromatography using a gradient of EtOAc/petroleum ether from 1/100 to 1/2 to afford 4-chloro-6-methylpyridine-2,3-diamine. LC-MS: 158.1 [M+H]⁺.

[00364] Steps C, D, and E: (R)-(7-Chloro-5-methyl-1H-imidazo[4,5-*b*]pyridin-2-yl)(5-methyl-7,8-dihydro-1,6-naphthyridin-6(5H)-yl)methanone was prepared from 4-chloro-6-methylpyridine-2,3-diamine according to the procedure of Example 35, Steps A, B, and C. LC-MS: 342.2 [M+H]⁺. ¹H NMR (400 MHz, DMSO-*d*₆) δ 8.30 – 8.52 (m, 1 H), 7.60 – 7.89 (m, 1 H), 7.36 – 7.43 (m, 1 H), 7.19 – 7.32 (m, 1 H), 5.63 – 6.24 (m, 1 H), 4.60 – 5.41 (m, 1 H), 3.43 –

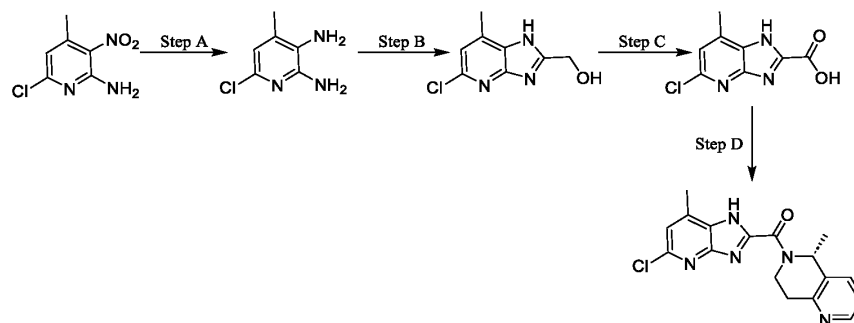
3.85 (m, 1 H), 3.10 – 3.26 (m, 1 H), 2.92 – 3.02 (m, 1 H), 2.56 – 2.64 (m, 3 H), 1.46 – 1.76 (m, 3 H).

Example 81: (R)-(6,7-Dichloro-1H-imidazo[4,5-b]pyridin-2-yl)(5-methyl-7,8-dihydro-1,6-naphthyridin-6(5H)-yl)methanone



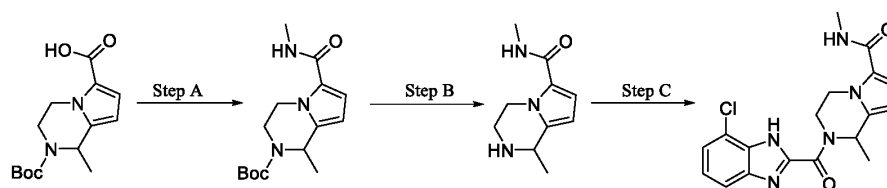
[00365] (R)-(6,7-Dichloro-1H-imidazo[4,5-b]pyridin-2-yl)(5-methyl-7,8-dihydro-1,6-naphthyridin-6(5H)-yl)methanone was prepared from 4,5-dichloro-3-nitropyridin-2-amine according to the procedure of Example 80, Steps B, C, D, and E. LC-MS: 362.0 [M+H]⁺. ¹H NMR (400 MHz, DMSO *d*₆) δ 14.35 (br s, 1H), 8.69 – 8.53 (m, 1H), 8.48 – 8.35 (m, 1H), 7.85 – 7.55 (m, 1H), 7.39 – 7.07 (m, 1H), 6.05 – 5.62 (m, 1H), 5.36 – 4.61 (m, 1H), 3.85 – 3.38 (m, 1H), 3.25 – 2.88 (m, 2H), 1.76 – 1.52 (m, 3H).

Example 82: (R)-(5-Chloro-7-methyl-1H-imidazo[4,5-b]pyridin-2-yl)(5-methyl-7,8-dihydro-1,6-naphthyridin-6(5H)-yl)methanone



[00366] (R)-(5-Chloro-7-methyl-1H-imidazo[4,5-b]pyridin-2-yl)(5-methyl-7,8-dihydro-1,6-naphthyridin-6(5H)-yl)methanone was prepared from 6-chloro-4-methyl-3-nitropyridin-2-amine according to the procedure of Example 80, Steps B, C, D, and E. LC-MS: 211.9 [M+H]⁺. ¹H NMR (400 MHz, DMSO *d*₆) δ 8.34 – 8.49 (m, 1 H), 7.59 – 7.87 (m, 1 H), 7.15 – 7.35 (m, 2 H), 5.62 – 6.39 (m, 1 H), 4.54 – 5.47 (m, 1 H), 3.38 – 3.76 (m, 1 H), 2.89 – 3.25 (m, 2 H), 2.55 – 2.72 (m, 3 H), 1.37 – 1.81 (m, 3 H).

Example 83: 2-(7-Chloro-1H-benzo[d]imidazole-2-carbonyl)-N,1-dimethyl-1,2,3,4-tetrahydropyrrolo[1,2-a]pyrazine-6-carboxamide

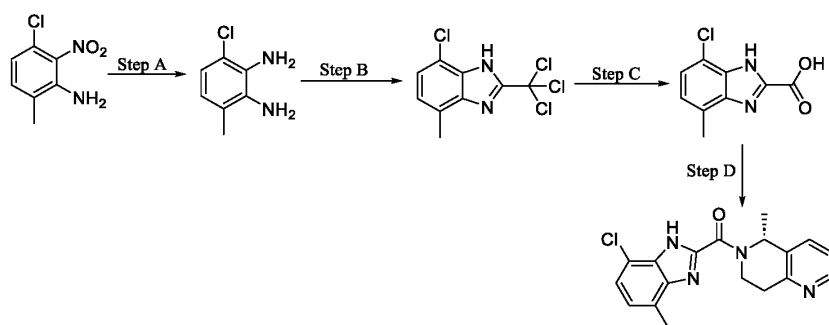


[00367] Step A: A mixture of 2-(tert-butoxycarbonyl)-1-methyl-1,2,3,4-tetrahydropyrrolo[1,2-a]pyrazine-6-carboxylic acid (150 mg, 0.535 mmol), methanamine (108 mg, 1.61 mmol), T₄P (771 mg, 1.07 mmol) and TEA (162 mg, 1.61 mmol) in DCM (3.00 mL) was stirred at 20 °C for 1 h. The reaction mixture was poured into H₂O (5.00 mL) and extracted with DCM (3.00 mL x 3). The combined organic layers were dried over Na₂SO₄, filtered, and concentrated under vacuum to give a residue which was purified by preparative TLC (EtOAc/petroleum = 1:1, R_f = 0.6) to afford tert-butyl 1-methyl-6-(methylcarbamoyl)-3,4-dihydropyrrolo[1,2-a]pyrazine-2(1H)-carboxylate. LC-MS: 238.2 [M+H]⁺.

[00368] Step B: To a solution of tert-butyl 1-methyl-6-(methylcarbamoyl)-3,4-dihydropyrrolo[1,2-a]pyrazine-2(1H)-carboxylate (40.0 mg, 0.136 mmol) in EtOAc (2.00 mL) was added HCl/EtOAc (4M, 4.40 mL). The resulting mixture was stirred at 20 °C for 1 h. The mixture was concentrated under vacuum at 30 °C to give N,1-dimethyl-1,2,3,4-tetrahydropyrrolo[1,2-a]pyrazine-6-carboxamide. LC-MS: 194.3 [M+H]⁺.

[00369] Step C: A mixture of N,1-dimethyl-1,2,3,4-tetrahydropyrrolo[1,2-a]pyrazine-6-carboxamide (25.0 mg, 0.129 mmol), 7-chloro-1H-benzo[d]imidazole-2-carboxylic acid (25.4 mg, 0.129 mmol), HATU (98.3 mg, 0.259 mmol) and DIEA (33.4 mg, 0.259 mmol) in DMF (1.00 mL) was stirred at 20 °C for 1 h. The reaction mixture was poured into H₂O (5.00 mL) and extracted with EtOAc (3.00 mL x 3). The combined organic layers were dried over Na₂SO₄, filtered, and concentrated under vacuum to give a residue which was purified by preparative HPLC (Phenomenex Luna C18 column (100 × 30 mm, 10 μm); flow rate: 25 mL/min; gradient: 25% – 55% B over 8 min; mobile phase A: 10 mM aqueous NH₄HCO₃, mobile phase B: acetonitrile) to afford 2-(7-chloro-1H-benzo[d]imidazole-2-carbonyl)-N,1-dimethyl-1,2,3,4-tetrahydropyrrolo[1,2-a]pyrazine-6-carboxamide. LC-MS: 370.2 [M+H]⁺. ¹H NMR (400 MHz, CDCl₃) δ 10.62 – 10.32 (m, 1H), 7.84 – 7.70 (m, 1H), 7.47 – 7.29 (m, 2H), 7.27 – 7.17 (m, 1H), 6.55 – 6.33 (m, 1H), 6.04 – 5.89 (m, 1H), 5.79 (br s, 1H), 5.07 – 4.81 (m, 1H), 4.46 – 4.15 (m, 1H), 3.63 (br d, J = 7.4 Hz, 1H), 2.94 (d, J = 4.9 Hz, 3H), 1.82 – 1.60 (m, 3H).

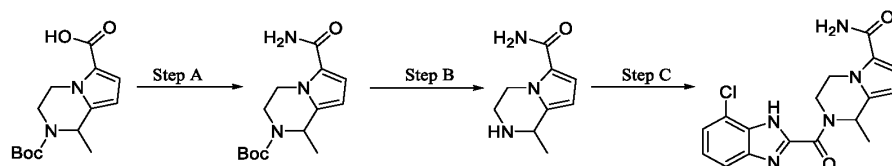
Example 84: (R)-(7-Chloro-4-methyl-1H-benzo[d]imidazol-2-yl)(5-methyl-7,8-dihydro-1,6-naphthyridin-6(5H)-yl)methanone



[00370] Step A: To a solution of 3-chloro-6-methyl-2-nitroaniline (500 mg, 2.68 mmol) in EtOAc (100 mL) was added SnCl_2 (4.84 g, 21.0 mmol). The mixture was stirred at 70 °C for 48 h. The mixture was diluted with EtOAc (100 mL), washed with saturated aqueous solution of NaHCO_3 (100 mL $\times$ 2), brine (50.0 mL), dried over MgSO_4 , and concentrated under reduced pressure to give a residue, which was purified by flash silica gel chromatography using a gradient of EtOAc/petroleum ether from 0/1 to 1/1 to afford 3-chloro-6-methylbenzene-1,2-diamine. LC-MS: 157.3 $[\text{M}+\text{H}]^+$.

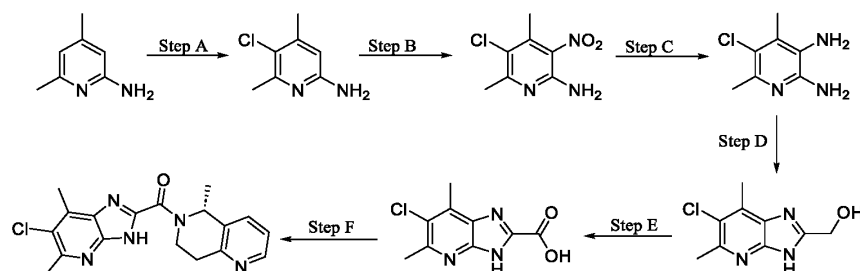
[00371] Steps B, C, and D: The title compound was prepared from 3-chloro-6-methylbenzene-1,2-diamine according to the procedure of Example 30, Steps A, B, and C to provide (R)-(7-chloro-4-methyl-1H-benzo[d]imidazol-2-yl)(5-methyl-7,8-dihydro-1,6-naphthyridin-6(5H)-yl)methanone. LC-MS: 341.1 $[\text{M}+\text{H}]^+$. ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ 8.92 – 8.22 (m, 2H), 8.07 – 7.72 (m, 1H), 7.37 – 7.03 (m, 2H), 6.54 – 5.86 (m, 1H), 5.62 – 4.73 (m, 2H), 3.79 – 3.67 (m, 2H), 3.49 – 3.20 (m, 3H), 1.92 – 1.38 (m, 3H).

Example 85: 2-(7-Chloro-1H-benzo[d]imidazole-2-carbonyl)-1-methyl-1,2,3,4-tetrahydropyrrolo[1,2-a]pyrazine-6-carboxamide



[00372] 2-(7-Chloro-1H-benzo[d]imidazole-2-carbonyl)-1-methyl-1,2,3,4-tetrahydropyrrolo[1,2-a]pyrazine-6-carboxamide was prepared from 2-(tert-butoxycarbonyl)-1-methyl-1,2,3,4-tetrahydropyrrolo[1,2-a]pyrazine-6-carboxylic acid according to the procedure of Example 83, Steps A, B, and C. LC-MS: 358.1 $[\text{M}+\text{H}]^+$. ^1H NMR (400 MHz, CDCl_3) δ 10.72 – 10.37 (m, 1H), 7.80 – 7.28 (m, 3H), 7.27 – 7.16 (m, 1H), 6.66 (d, $J = 4.0$ Hz, 1H), 6.58 – 5.86 (m, 2H), 5.63 – 5.14 (m, 2H), 5.11 – 4.89 (m, 1H), 4.40 – 4.16 (m, 1H), 3.92 – 3.38 (m, 1H), 1.83 – 1.61 (m, 3H). LC-MS: 238.2 $[\text{M}+\text{H}]^+$.

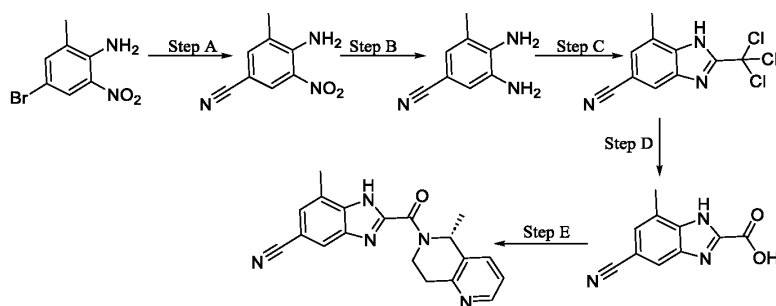
Example 86: (R)-(6-Chloro-5,7-dimethyl-3H-imidazo[4,5-b]pyridin-2-yl)(5-methyl-7,8-dihydro-1,6-naphthyridin-6(5H)-yl)methanone



[00373] Step A: To a solution of 4,6-dimethylpyridin-2-amine (8.00 g, 65.5 mmol) in acetonitrile (15.0 mL) was added NCS (9.18 g, 68.8 mmol) at 0 °C. The mixture was stirred at 10 °C for 12 h. The reaction mixture was poured into H₂O (60.0 mL) and extracted with EtOAc (50.0 mL x 2). The combined organic layers were dried over Na₂SO₄, filtered, and concentrated under vacuum to give a residue which was purified by flash silica gel chromatography using a gradient of EtOAc/petroleum ether from 0/1 to 1/1 to afford 5-chloro-4,6-dimethylpyridin-2-amine. LC-MS: 157.2 [M+H]⁺.

[00374] Steps B, C, D, E, and F: (R)-(6-Chloro-5,7-dimethyl-3H-imidazo[4,5-b]pyridin-2-yl)(5-methyl-7,8-dihydro-1,6-naphthyridin-6(5H)-yl)methanone was prepared from 5-chloro-4,6-dimethylpyridin-2-amine according to the procedure of Example 80, Steps A, B, C, D, and E. LC-MS: 356.1 [M+H]⁺. ¹H NMR (400 MHz, CDCl₃) δ 11.03 – 10.54 (m, 1H), 8.48 (br d, *J* = 4.1 Hz, 1H), 7.52 (br d, *J* = 7.5 Hz, 1H), 7.24 – 7.16 (m, 1H), 7.11 – 6.20 (m, 1H), 6.01 – 4.81 (m, 1H), 3.88 – 3.02 (m, 3H), 2.85 – 2.56 (m, 6H), 1.79 (d, *J* = 6.6 Hz, 1H), 1.63 (br s, 2H).

Example 87: (R)-7-Methyl-2-(5-methyl-5,6,7,8-tetrahydro-1,6-naphthyridine-6-carbonyl)-1H-benzo[d]imidazole-5-carbonitrile

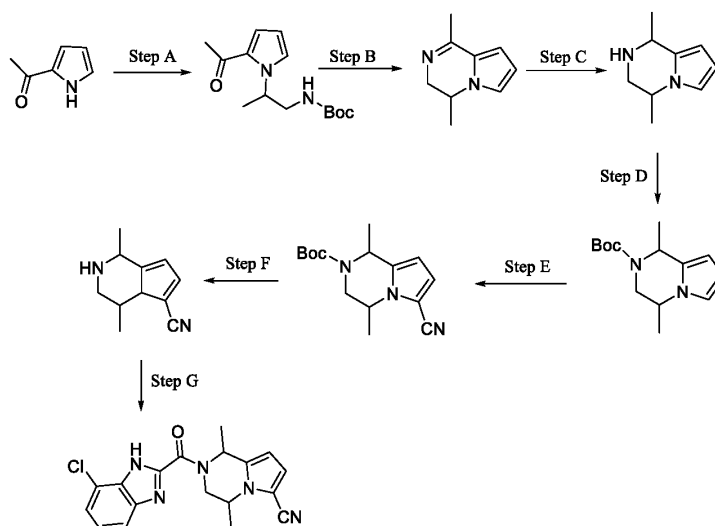


[00375] Step A: A mixture of 4-bromo-2-methyl-6-nitroaniline (1.00 g, 4.33 mmol), CuCN (581 mg, 6.49 mmol) in DMF (15.0 mL) was degassed and purged with N₂ for 3 times, and then the mixture was stirred at 140 °C for 2 h under nitrogen. The mixture was poured into water (15.0 mL) and extracted with EtOAc (15.0 mL x 2). The combined organic layers were dried

over Na_2SO_4 , filtered, and concentrated under vacuum to give a residue which was purified by flash silica gel chromatography using a gradient of EtOAc/petroleum ether from 0/1 to 1/0 to afford 4-amino-3-methyl-5-nitrobenzonitrile. LC-MS: 177.9 $[\text{M}+\text{H}]^+$.

[00376] Steps B, C, D, and E: Methyl-2-(5-methyl-5,6,7,8-tetrahydro-1,6-naphthyridine-6-carbonyl)-1H-benzo[d]imidazole-5-carbonitrile was prepared from 4-amino-3-methyl-5-nitrobenzonitrile according to the procedure of Example 84, Steps A, B, C, and D. LC-MS: 332.1 $[\text{M}+\text{H}]^+$. ^1H NMR (400 MHz, CDCl_3) δ 11.22 - 10.71 (m, 1H), 8.53 - 8.43 (m, 1H), 8.13 - 7.69 (m, 1H), 7.62 - 7.36 (m, 2H), 7.21 (dd, $J = 4.6, 7.8$ Hz, 1H), 7.15 - 6.19 (m, 1H), 5.95 - 4.87 (m, 1H), 3.94 - 3.03 (m, 3H), 2.76 - 2.53 (m, 3H), 1.85 - 1.63 (m, 3H).

Example 88: 2-(7-Chloro-1H-benzo[d]imidazole-2-carbonyl)-1,4-dimethyl-1,2,3,4-tetrahydropyrrolo[1,2-a]pyrazine-6-carbonitrile



[00377] Step A: To a solution of 1-(1H-pyrrol-2-yl)ethan-1-one (750 mg, 6.87 mmol) in DMF (20.0 mL) was added NaH (550 mg, 13.8 mmol, 60% purity) and the mixture was stirred at 20 °C for 15 min. To the slightly yellow solution was added tert-butyl 5-methyl-1,2,3-oxathiazolidine-3-carboxylate 2,2-dioxide (1.96 g, 8.25 mmol) and the mixture was stirred at 20 °C for 18 h. The reaction mixture was poured into water (20.0 mL) and extracted with EtOAc (20.0 mL x 3). The combined organic layers were dried over Na_2SO_4 , filtered, and concentrated under vacuum to give a residue which was purified by flash silica gel chromatography using a gradient of EtOAc/petroleum ether from 0/1 to 1/10 to afford tert-butyl (2-(2-acetyl-1H-pyrrol-1-yl)propyl)carbamate. LC-MS: 211.2 $[\text{M}+\text{H}]^+$.

[00378] Step B: To a solution of tert-butyl (2-(2-acetyl-1H-pyrrol-1-yl)propyl)carbamate (700 mg, 0.799 mmol) in EtOAc (5.00 mL) was added HCl/EtOAc (4.0 M, 20.0 mL). The resulting

mixture was stirred at 20 °C for 1 h. The mixture was concentrated under vacuum to give 1,4-dimethyl-3,4-dihydropyrrolo[1,2-a]pyrazine. LC-MS: 149.3 [M+H]⁺.

[00379] Step C: To a solution of 1,4-dimethyl-3,4-dihydropyrrolo[1,2-a]pyrazine (500 mg, 3.37 mmol) in MeOH (20.0 mL) was added NaBH₄ (510 mg, 13.5 mmol). The mixture was stirred at 20 °C for 30 min. The reaction mixture was poured into water (10.0 mL). 1,4-dimethyl-1,2,3,4-tetrahydropyrrolo[1,2-a]pyrazine was obtained in MeOH/H₂O (30 mL). LC-MS: 151.3 [M+H]⁺.

[00380] Step D: To a solution of 1,4-dimethyl-1,2,3,4-tetrahydropyrrolo[1,2-a]pyrazine (500 mg, 3.33 mmol) in MeOH (20.0 mL) and H₂O (10.0 mL) was added Boc₂O (799 mg, 3.66 mmol) and K₂CO₃ (920 mg, 6.66 mmol). The mixture was stirred at 20 °C for 1 h. The reaction mixture was poured into water (5.00 mL) and extracted with EtOAc (5.00 mL x 3). The combined organic layers were dried over Na₂SO₄, filtered, and concentrated under vacuum to give a residue which was purified by flash silica gel chromatography using a gradient of EtOAc/petroleum ether from 0/1 to 1/10 to afford tert-butyl 1,4-dimethyl-3,4-dihydropyrrolo[1,2-a]pyrazine-2(1H)-carboxylate. LC-MS: 251.2 [M+H]⁺.

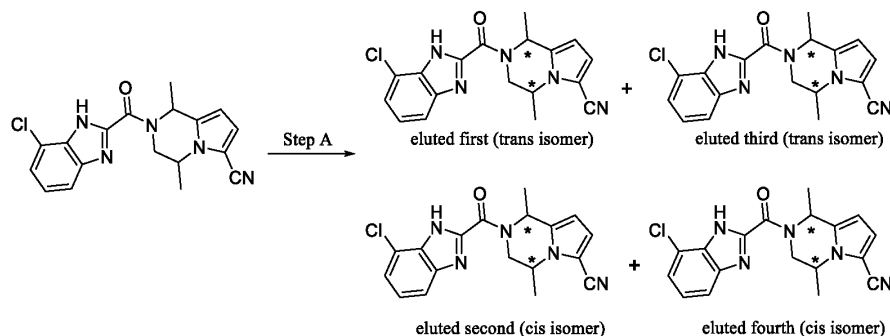
[00381] Step E: To a solution of tert-butyl 1,4-dimethyl-3,4-dihydropyrrolo[1,2-a]pyrazine-2(1H)-carboxylate (320 mg, 1.28 mmol) in DCM (20.0 mL) was added sulfurisocyanatidic chloride (199 mg, 1.41 mmol). The mixture was degassed and purged with nitrogen three times and stirred at 0 °C for 1 h under a nitrogen atmosphere. Then DMF (934 mg, 12.8 mmol) was added dropwise to the mixture, cooled to -10 °C. The resulting mixture was stirred at 20 °C for 5 h. The reaction mixture was poured into water (10.0 mL) and extracted with EtOAc (10.0 mL x 5). The combined organic layers were dried over Na₂SO₄, filtered, and concentrated under vacuum to give a residue which was purified by flash silica gel chromatography using a gradient of EtOAc/petroleum ether from 0/1 to 1/10 to afford tert-butyl 6-cyano-1,4-dimethyl-3,4-dihydropyrrolo[1,2-a]pyrazine-2(1H)-carboxylate. LC-MS: 276.3 [M+H]⁺.

[00382] Step F: To a solution of tert-butyl 6-cyano-1,4-dimethyl-3,4-dihydropyrrolo[1,2-a]pyrazine-2(1H)-carboxylate (220 mg, 0.800 mmol) in EtOAc (2.00 mL) was added HCl/EtOAc (4.0 M, 10.0 mL). The resulting mixture was stirred at 20 °C for 1 h. The mixture was concentrated under vacuum at 30 °C to give 1,4-dimethyl-2,3,4,4a-tetrahydro-1H-cyclopenta[c]pyridine-5-carbonitrile. ¹H NMR (400 MHz, DMSO *d*₆) δ 7.09 (dd, *J* = 4.1, 12.5 Hz, 1H), 6.32 – 6.23 (m, 1H), 4.81 – 4.39 (m, 2H), 3.85 – 3.54 (m, 1H), 3.30 (br dd, *J* = 8.9, 13.3 Hz, 1H), 1.67 – 1.55 (m, 6H).

[00383] Step G: To a solution of 1,4-dimethyl-2,3,4,4a-tetrahydro-1H-cyclopenta[c]pyridine-5-carbonitrile (170 mg, 0.803 mmol), 7-chloro-1H-benzo[d]imidazole-2-carboxylic acid (158 mg, 0.803 mmol) in DMF (5.00 mL) was added DIEA (311 mg, 2.41 mmol) and HATU (153 mg,

0.402 mmol). The mixture was stirred at 20 °C for 1 h. The reaction mixture was poured into H₂O (10.0 mL), then the precipitate was formed. The reaction mixture was filtered. The filter cake was washed with 10.0 mL of H₂O and dried in vacuum to give 2-(7-chloro-1H-benzo[d]imidazole-2-carbonyl)-1,4-dimethyl-1,2,3,4-tetrahydropyrrolo[1,2-a]pyrazine-6-carbonitrile. LC-MS: 354.1 [M+H]⁺. ¹H NMR (400 MHz, DMSO *d*₆) δ 13.81 – 13.29 (m, 1H), 7.53 (br d, *J* = 7.9 Hz, 1H), 7.45 – 7.25 (m, 2H), 7.09 – 6.95 (m, 1H), 6.44 – 6.04 (m, 1H), 6.02 – 5.67 (m, 1H), 4.90 – 3.56 (m, 2H), 3.32 – 3.05 (m, 1H), 1.73 – 1.65 (m, 2H), 1.53 (br d, *J* = 6.8 Hz, 1H), 1.42 – 1.20 (m, 3H).

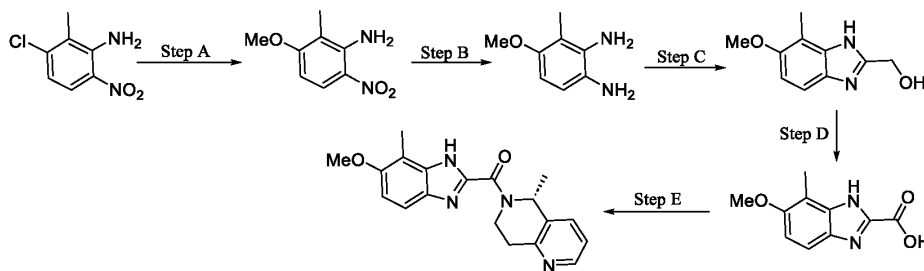
Examples 88A, 88B, 88C, and 88D: *trans*-(1*S*,4*R*) or (1*R*,4*S*)-2-(7-Chloro-1H-benzo[d]imidazole-2-carbonyl)-1,4-dimethyl-1,2,3,4-tetrahydropyrrolo[1,2-a]pyrazine-6-carbonitrile, *cis*-(1*S*,4*S*) or (1*R*,4*R*)-2-(7-Chloro-1H-benzo[d]imidazole-2-carbonyl)-1,4-dimethyl-1,2,3,4-tetrahydropyrrolo[1,2-a]pyrazine-6-carbonitrile, *trans*-(1*S*,4*R*) or (1*R*,4*S*)-2-(7-Chloro-1H-benzo[d]imidazole-2-carbonyl)-1,4-dimethyl-1,2,3,4-tetrahydropyrrolo[1,2-a]pyrazine-6-carbonitrile, and *cis*-(1*S*,4*S*) or (1*R*,4*R*)-2-(7-Chloro-1H-benzo[d]imidazole-2-carbonyl)-1,4-dimethyl-1,2,3,4-tetrahydropyrrolo[1,2-a]pyrazine-6-carbonitrile



[00384] Step A: 2-(7-Chloro-1H-benzo[d]imidazole-2-carbonyl)-1,4-dimethyl-1,2,3,4-tetrahydropyrrolo[1,2-a]pyrazine-6-carbonitrile (**Example 88**) (120 mg, 340 μmol) was further separated (ChiralPak IH (250 × 30 mm, 10 μm); flow rate: 64 mL/min; gradient: 45% B over 4 min; mobile phase A: CO₂, mobile phase B: IPA (0.1% NH₃H₂O)) to afford a first eluted compound and a fourth eluted compound. *rac*-2-(7-Chloro-1H-benzo[d]imidazole-2-carbonyl)-1,4-dimethyl-1,2,3,4-tetrahydropyrrolo[1,2-a]pyrazine-6-carbonitrile (50.0 mg) was further separated (DAICEL CHIRALPAK IC (250 × 30 mm, 10 μm); flow rate: 64 mL/min; gradient: 35% B over 4 min; mobile phase A: CO₂, mobile phase B: MeOH (0.1% NH₃H₂O)) to afford a second eluted compound and a third eluted compound. First eluted compound (**Example 88A**): LC-MS: 354.1 [M+H]⁺. ¹H NMR (400 MHz, DMSO *d*₆) δ 13.86 – 13.41 (m, 1H), 7.77 – 7.22 (m, 3H), 7.12 – 6.59 (m, 1H), 6.29 – 6.07 (m, 1H), 6.04 – 5.73 (m, 1H), 4.85 – 4.54 (m, 1H),

3.92 (dd, $J = 3.3, 14.3$ Hz, 1H), 3.42 – 3.33 (m, 1H), 1.73 – 1.30 (m, 6H). Second eluted compound (**Example 88B**): LC-MS: 354.1 $[M+H]^+$. ^1H NMR (400 MHz, DMSO- d_6) δ 13.77 – 13.39 (m, 1H), 7.75 – 6.94 (m, 4H), 6.78 – 6.09 (m, 1H), 5.96 – 5.55 (m, 1H), 4.91 – 4.33 (m, 1H), 3.80 – 3.32 (m, 2H), 1.79 – 1.48 (m, 6H). Third eluted compound (**Example 88C**): LC-MS: 354.1 $[M+H]^+$. ^1H NMR (400 MHz, DMSO d_6) δ 13.63 (br d, $J = 2.3$ Hz, 1H), 7.61 – 7.24 (m, 3H), 7.07 – 6.61 (m, 1H), 6.28 – 6.07 (m, 1H), 6.05 – 5.69 (m, 1H), 4.85 – 4.47 (m, 1H), 4.03 – 3.52 (m, 1H), 3.35 (br s, 1H), 1.80 – 1.27 (m, 6H). Fourth eluted compound (**Example 88D**): LC-MS: 354.1 $[M+H]^+$. ^1H NMR (400 MHz, DMSO- d_6) δ 13.58 (br s, 1H), 7.88 – 6.96 (m, 4H), 6.30 – 6.05 (m, 1H), 5.79 (br d, $J = 1.5$ Hz, 1H), 4.92 – 4.33 (m, 1H), 3.86 – 3.53 (m, 1H), 3.37 – 3.33 (m, 1H), 1.84 – 1.48 (m, 6H). The absolute stereochemistry for the cis and trans compounds was not determined.

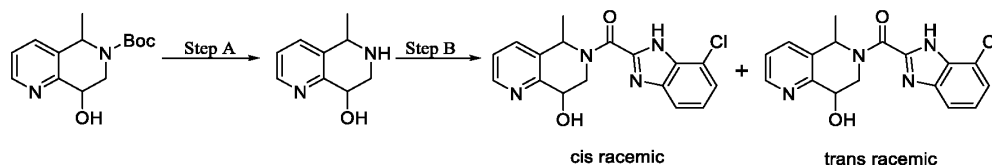
Example 89: (*R*)-(6-Methoxy-7-methyl-1H-benzo[d]imidazol-2-yl)(5-methyl-7,8-dihydro-1,6-naphthyridin-6(5H)-yl)methanone



[00385] Step A: To a solution of 3-chloro-2-methyl-6-nitro-aniline (1.00 g, 5.00 mmol) in MeOH (10.0 mL) was added MeONa (19.3 g, 107 mmol, 30% purity). The mixture was stirred at 70 °C for 12 h. The reaction mixture was concentrated, diluted with 1N HCl (30.0 mL) and extracted with EtOAc (50.0 mL x 3). The combined organic layers were dried over Na_2SO_4 , filtered and concentrated under reduced pressure to give 3-methoxy-2-methyl-6-nitro-aniline. LC-MS: 183.3 $[M+H]^+$.

[00386] Steps B, C, D, and E: (*R*)-(6-methoxy-7-methyl-1H-benzo[d]imidazol-2-yl)(5-methyl-7,8-dihydro-1,6-naphthyridin-6(5H)-yl)methanone was prepared from 3-methoxy-2-methyl-6-nitro-aniline according to the procedure of Example 80, Steps B, C, D, and E. LC-MS: 337.1 $[M+H]^+$. ^1H NMR (400 MHz, DMSO- d_6) δ 8.82 – 8.72 (m, 1H), 8.65 – 8.48 (m, 1H), 8.01 – 7.85 (m, 1H), 7.59 – 7.46 (m, 1H), 7.19 – 7.06 (m, 1H), 6.00 – 5.86 (m, 1H), 5.47 – 5.34 (m, 1H), 4.79 (br dd, $J = 5.7, 13.3$ Hz, 1H), 3.86 – 3.83 (m, 3H), 3.56 – 3.32 (m, 2H), 2.45 – 2.37 (m, 3H), 1.79 – 1.57 (m, 3H).

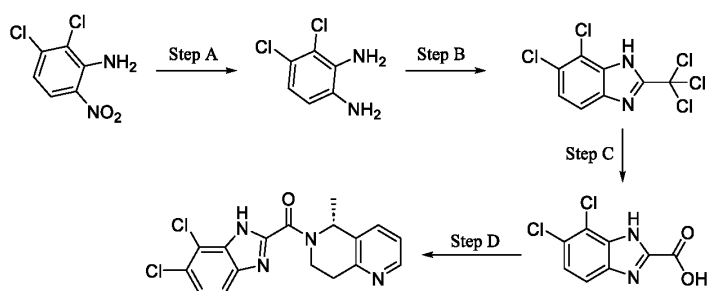
Example 90A and 90B: (7-Chloro-1H-benzo[d]imidazol-2-yl)((cis)-8-hydroxy-5-methyl-7,8-dihydro-1,6-naphthyridin-6(5H)-yl)methanone and (7-Chloro-1H-benzo[d]imidazol-2-yl)((trans)-8-hydroxy-5-methyl-7,8-dihydro-1,6-naphthyridin-6(5H)-yl)methanone



[00387] Step A: A solution of tert-butyl 8-hydroxy-5-methyl-7,8-dihydro-1,6-naphthyridine-6(5H)-carboxylate (100 mg, 0.378 mmol) in 4M HCl/EtOAc (1.00 mL) was stirred at 25 °C for 0.5 h. The reaction mixture was concentrated under reduced pressure to give 5-methyl-5,6,7,8-tetrahydro-1,6-naphthyridin-8-ol. LC-MS: 165.3 [M+H]⁺.

[00388] Step B: To a solution of 5-methyl-5,6,7,8-tetrahydro-1,6-naphthyridin-8-ol (42.0 mg, 0.254 mmol) and 7-chloro-1H-benzo[d]imidazole-2-carboxylic acid (50.0 mg, 0.254 mmol) in DMF (1.00 mL) was added DIEA (98.6 mg, 0.763 mmol) and HATU (48.0 mg, 0.127 mmol). The mixture was stirred at 25 °C for 2 h. The reaction mixture was concentrated under reduced pressure to give a residue which was purified by preparative HPLC (Phenomenex luna C18 100 x 40mm x 5 μm; mobile phase: [H₂O(0.04% HCl)-ACN]; gradient: 10%-40% B over 8.0 min) to afford (7-chloro-1H-benzo[d]imidazol-2-yl)((cis)-8-hydroxy-5-methyl-7,8-dihydro-1,6-naphthyridin-6(5H)-yl)methanone and (7-chloro-1H-benzo[d]imidazol-2-yl)((trans)-8-hydroxy-5-methyl-7,8-dihydro-1,6-naphthyridin-6(5H)-yl)methanone. Cis compound (**Example 90A**): LC-MS: 343.1 [M+H]⁺. ¹H NMR (400 MHz, DMSO-*d*₆) δ 8.81 – 8.68 (m, 1H), 8.61 – 8.47 (m, 1H), 7.98 (s, 1H), 7.62 – 7.55 (m, 1H), 7.40 (t, *J* = 6.9 Hz, 1H), 7.37 – 7.29 (m, 1H), 5.94 (q, *J* = 6.5 Hz, 1H), 5.18 – 4.81 (m, 2H), 3.64 – 3.53 (m, 1H), 3.40 – 3.22 (m, 1H), 1.91 – 1.56 (m, 3H). Trans compound (**Example 90B**): LC-MS: 343.1 [M+H]⁺. ¹H NMR (400 MHz, DMSO-*d*₆) δ 8.73 – 8.64 (m, 1H), 8.30 – 8.17 (m, 1H), 7.74 – 7.64 (m, 1H), 7.60 – 7.52 (m, 1H), 7.41 – 7.37 (m, 1H), 7.35 – 7.30 (m, 1H), 6.09 – 5.91 (m, 1H), 5.83 – 5.65 (m, 1H), 4.97 – 4.67 (m, 2H), 3.90 (br d, *J* = 1.8 Hz, 1H), 1.68 – 1.52 (m, 3H).

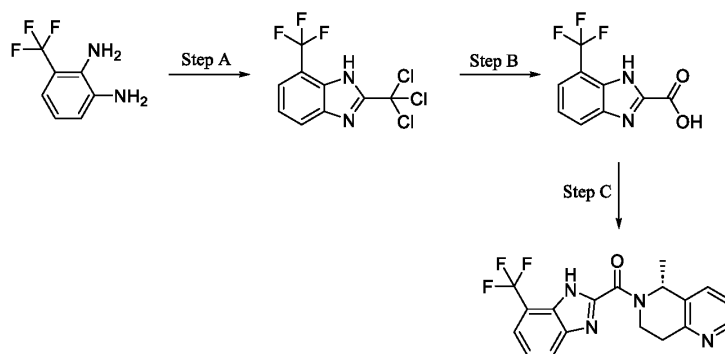
Example 91: (R)-(6,7-Dichloro-1H-benzo[d]imidazol-2-yl)(5-methyl-7,8-dihydro-1,6-naphthyridin-6(5H)-yl)methanone



[00389] Step A: To a solution of 2,3-dichloro-6-nitroaniline (1.00 g, 4.83 mmol) in MeOH (10.0 mL) was added Fe (1.35 g, 24.0 mmol) and NH_4Cl (1.29 g, 24.0 mmol). The mixture was stirred at 70 °C for 1 h. The reaction mixture was allowed to cool to room temperature. The reaction mixture was filtered, concentrated under reduced pressure to give a residue which was purified by flash silica gel chromatography using a gradient of EtOAc/petroleum ether from 0/1 to 1/1 to afford 3,4-dichlorobenzene-1,2-diamine. LC-MS: 177.2 $[\text{M}+\text{H}]^+$.

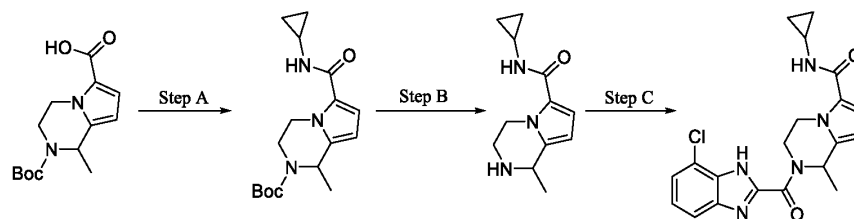
[00390] Steps B, C, and D: (R)-(6,7-Dichloro-1H-benzo[d]imidazol-2-yl)(5-methyl-7,8-dihydro-1,6-naphthyridin-6(5H)-yl)methanone was prepared from 3,4-dichlorobenzene-1,2-diamine according to the procedure of Example 30, Steps A, B, and C. LC-MS: 361.0 $[\text{M}+\text{H}]^+$. ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ 8.81 – 8.63 (m, 1H), 8.57 – 8.30 (m, 1H), 7.94 – 7.68 (m, 1H), 7.63 – 7.41 (m, 2H), 6.00 – 5.58 (m, 1H), 3.49 – 3.19 (m, 4H), 1.87 – 1.51 (m, 3H).

Example 92: (R)-(5-Methyl-7,8-dihydro-1,6-naphthyridin-6(5H)-yl)(7-(trifluoromethyl)-1H-benzo[d]imidazol-2-yl)methanone



[00391] (R)-(5-Methyl-7,8-dihydro-1,6-naphthyridin-6(5H)-yl)(7-(trifluoromethyl)-1H-benzo[d]imidazol-2-yl)methanone was prepared from 3-(trifluoromethyl)benzene-1,2-diamine according to the procedure of Example 30, Steps A, B, and C. LC-MS: 361.1 $[\text{M}+\text{H}]^+$. ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ 8.80 – 8.25 (m, 2H), 7.92 – 7.48 (m, 4H), 6.69 – 5.91 (m, 1H), 5.64 – 4.79 (m, 1H), 3.78 – 3.70 (m, 1H), 3.49 – 3.38 (m, 1H), 3.24 (br d, $J = 15.1$ Hz, 1H), 1.84 – 1.49 (m, 3H).

Example 93: 2-(7-Chloro-1H-benzo[d]imidazole-2-carbonyl)-N-cyclopropyl-1-methyl-1,2,3,4-tetrahydropyrrolo[1,2-a]pyrazine-6-carboxamide

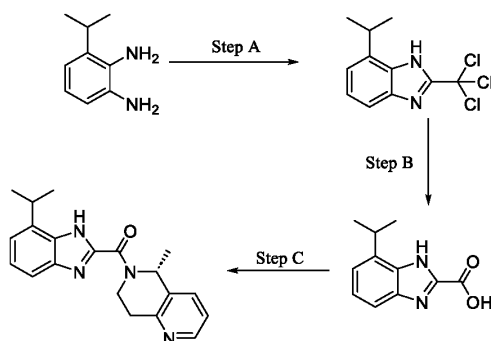


[00392] Step A: A mixture of 2-(tert-butoxycarbonyl)-1-methyl-1,2,3,4-tetrahydropyrrolo[1,2-a]pyrazine-6-carboxylic acid (200 mg, 0.713 mmol), cyclopropanamine (40.7 mg, 0.713 mmol), HATU (542 mg, 1.43 mmol) and DIEA (276 mg, 2.14 mmol) in DMF (2.00 mL) was stirred at 20 °C for 1 h. The reaction mixture was poured into H₂O (5.00 mL) and extracted with DCM (5.00 mL x 4). The combined organic layers were dried over Na₂SO₄, filtered, and concentrated under vacuum to give a residue which was purified by flash silica gel chromatography using a gradient of EtOAc/petroleum ether from 1/100 to 1/0 to afford tert-butyl 6-(cyclopropylcarbamoyl)-1-methyl-3,4-dihydropyrrolo[1,2-a]pyrazine-2(1H)-carboxylate. LC-MS: 264.2 [M+H]⁺.

[00393] Step B: To a solution of tert-butyl 6-(cyclopropylcarbamoyl)-1-methyl-3,4-dihydropyrrolo[1,2-a]pyrazine-2(1H)-carboxylate (200 mg, 0.626 mmol) in EtOAc (2.00 mL) was added HCl/EtOAc (4M, 20.0 mL). The mixture was stirred at 20 °C for 1 h. The mixture was concentrated under vacuum at 30 °C to give N-cyclopropyl-1-methyl-1,2,3,4-tetrahydropyrrolo[1,2-a]pyrazine-6-carboxamide. LC-MS: 220.3 [M+H]⁺.

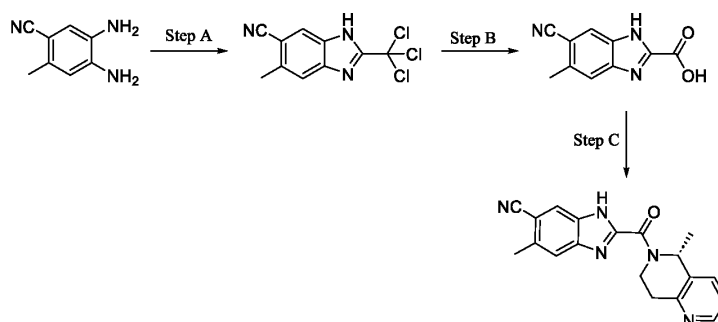
[00394] Step C: A mixture of N-cyclopropyl-1-methyl-1,2,3,4-tetrahydropyrrolo[1,2-a]pyrazine-6-carboxamide (50.0 mg, 0.228 mmol), 7-chloro-1H-benzo[d]imidazole-2-carboxylic acid (44.8 mg, 0.228 mmol), HATU (173 mg, 0.456 mmol) and DIEA (58.9 mg, 0.456 mmol) in DMF (1.00 mL) was stirred at 20 °C for 1 h. The reaction mixture was poured into H₂O (5.00 mL) and extracted with EtOAc (3.00 mL x 3). The combined organic layers were dried over Na₂SO₄, filtered, and concentrated under vacuum to give a residue which was purified by preparative HPLC (Phenomenex Luna C18 column (100 × 40 mm, 5 μm); flow rate: 25 mL/min; gradient: 25% – 55% B over 8 min; mobile phase A: 0.04% aqueous HCl, mobile phase B: acetonitrile) to afford 2-(7-chloro-1H-benzo[d]imidazole-2-carbonyl)-N-cyclopropyl-1-methyl-1,2,3,4-tetrahydropyrrolo[1,2-a]pyrazine-6-carboxamide. LC-MS: 398.1 [M+H]⁺. ¹H NMR (400 MHz, DMSO-*d*₆) δ 7.93 (br s, 1H), 7.56 (br d, *J* = 7.8 Hz, 1H), 7.42 – 7.28 (m, 2H), 6.87 – 6.53 (m, 1H), 6.09 – 5.94 (m, 1H), 5.81 – 5.60 (m, 1H), 4.85 – 4.63 (m, 1H), 4.19 – 3.97 (m, 1H), 3.82 – 3.65 (m, 2H), 2.72 (dt, *J* = 3.6, 7.3 Hz, 1H), 1.71 – 1.44 (m, 3H), 0.72 – 0.38 (m, 4H).

Example 94: (R)-(7-Isopropyl-1H-benzo[d]imidazol-2-yl)(5-methyl-7,8-dihydro-1,6-naphthyridin-6(5H)-yl)methanone



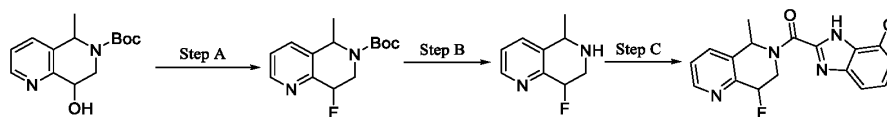
[00395] (R)-(7-Isopropyl-1H-benzo[d]imidazol-2-yl)(5-methyl-7,8-dihydro-1,6-naphthyridin-6(5H)-yl)methanone was prepared from 3-isopropylbenzene-1,2-diamine according to the procedure of Example 30, Steps A, B, and C. LC-MS: 335.1 $[M+H]^+$. 1H NMR (400 MHz, DMSO- d_6) δ 13.34 – 12.98 (m, 1H), 8.58 – 8.30 (m, 1H), 7.87 – 7.53 (m, 1H), 7.44 – 6.99 (m, 4H), 6.81 – 4.57 (m, 2H), 3.78 – 3.35 (m, 2H), 3.28 – 3.12 (m, 1H), 3.06 – 2.91 (m, 1H), 1.85 – 1.13 (m, 9H).

Example 95: (R)-5-methyl-2-(5-methyl-5,6,7,8-tetrahydro-1,6-naphthyridine-6-carbonyl)-1H-benzo[d]imidazole-6-carbonitrile



[00396] (R)-5-Methyl-2-(5-methyl-5,6,7,8-tetrahydro-1,6-naphthyridine-6-carbonyl)-1H-benzo[d]imidazole-6-carbonitrile was prepared from 4,5-diamino-2-methylbenzonitrile according to the procedure of Example 30, Steps A, B, and C. LC-MS: 332.1 $[M+H]^+$. 1H NMR (400 MHz, $CDCl_3$) δ 11.06 – 10.37 (m, 1H), 8.62 – 8.38 (m, 1H), 8.18 (s, 1H), 7.86 – 7.53 (m, 1H), 7.45 (s, 1H), 7.23 (br dd, J = 4.8, 7.4 Hz, 1H), 6.43 – 6.13 (m, 1H), 5.93 – 4.89 (m, 1H), 3.94 – 2.91 (m, 3H), 2.69 (s, 3H), 1.82 – 1.62 (m, 3H).

Example 96: (7-Chloro-1H-benzo[d]imidazol-2-yl)(8-fluoro-5-methyl-7,8-dihydro-1,6-naphthyridin-6(5H)-yl)methanone

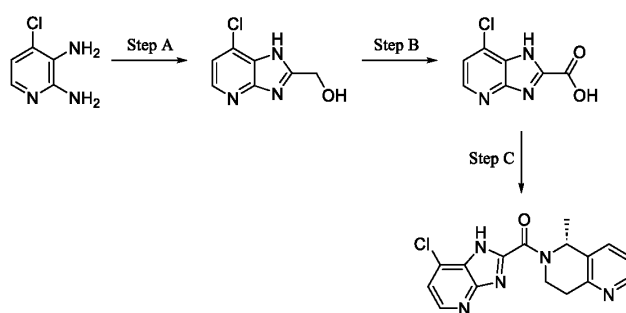


[00397] Step A: To a solution of *tert*-butyl 8-hydroxy-5-methyl-7,8-dihydro-1,6-naphthyridine-6(5*H*)-carboxylate (200 mg, 0.757 mmol) in DCM (2.00 mL) was added DAST (610 mg, 4 mmol) at -78 °C. The mixture was stirred at 25 °C for 5 h under nitrogen atmosphere. The reaction mixture was concentrated, diluted with saturated NaHCO₃ aqueous (10.0 mL) and extracted with EtOAc (10.0 mL x 3). The combined organic layers were dried over Na₂SO₄, filtered and concentrated under reduced pressure to give *tert*-butyl 8-fluoro-5-methyl-7,8-dihydro-1,6-naphthyridine-6(5*H*)-carboxylate. LC-MS: 267.2 [M+H]⁺.

[00398] Step B: A solution of *tert*-butyl 8-fluoro-5-methyl-7,8-dihydro-1,6-naphthyridine-6(5*H*)-carboxylate (80 mg, 0.300 mmol) in 4M HCl/EtOAc (3.00 mL) was stirred at 25 °C for 0.5 h. The reaction mixture was concentrated under reduced pressure to give 8-fluoro-5-methyl-5,6,7,8-tetrahydro-1,6-naphthyridine. LC-MS: 167.3 [M+H]⁺.

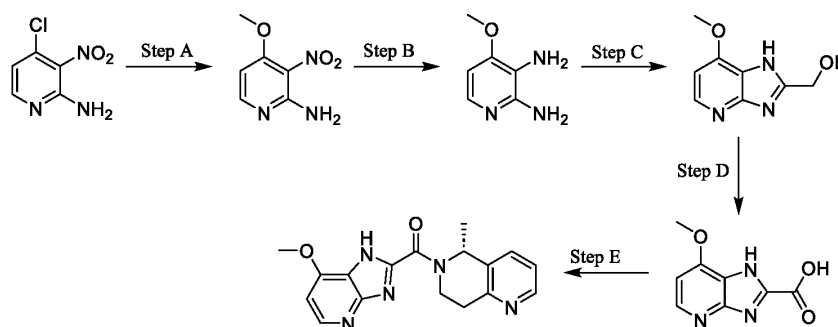
[00399] Step C: To a solution of 8-fluoro-5-methyl-5,6,7,8-tetrahydro-1,6-naphthyridine (42.0 mg, 0.254 mmol) and 7-chloro-1*H*-benzo[*d*]imidazole-2-carboxylic acid (50.0 mg, 0.254 mmol) in DMF (1.00 mL) was added DIEA (99.0 mg, 0.763 mmol) and HATU (48.0 mg, 0.127 mmol). The mixture was stirred at 25 °C for 12 h. The mixture was poured into H₂O (10.0 mL) and extracted with EtOAc (10.0 mL x 3). The combined organic layers were dried over Na₂SO₄, filtered, and concentrated under vacuum to give a residue which was purified by preparative HPLC (Phenomenex luna C18 100 x 40mm x 5 μm; mobile phase: [H₂O(0.04% HCl)-ACN]; gradient: 25%-65% B over 8.0 min) to afford (7-chloro-1*H*-benzo[*d*]imidazol-2-yl)(8-fluoro-5-methyl-7,8-dihydro-1,6-naphthyridin-6(5*H*)-yl)methanone. LC-MS: 345.1 [M+H]⁺. ¹H NMR (400 MHz, DMSO-*d*₆) δ 8.73 - 8.53 (m, 1H), 8.12 - 7.92 (m, 1H), 7.64 - 7.50 (m, 2H), 7.47 - 7.28 (m, 2H), 6.75 - 6.28 (m, 1H), 6.10 - 5.90 (m, 1H), 5.80 - 5.55 (m, 1H), 5.23 - 4.89 (m, 1H), 1.69 - 1.54 (m, 3H).

Example 97: (R)-(7-chloro-1*H*-imidazo[4,5-*b*]pyridin-2-yl)(5-methyl-7,8-dihydro-1,6-naphthyridin-6(5*H*)-yl)methanone



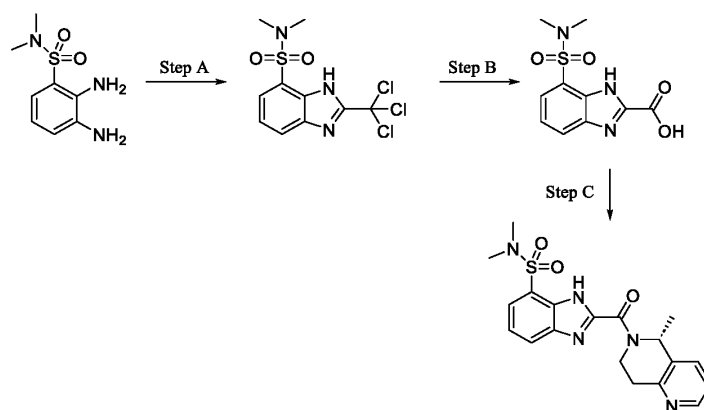
[00400] (R)-(7-Chloro-1H-imidazo[4,5-b]pyridin-2-yl)(5-methyl-7,8-dihydro-1,6-naphthyridin-6(5H)-yl)methanone was prepared from 4-chloropyridine-2,3-diamine according to the procedure of Example 35, Steps A, B, and C. LC-MS: 328.0 [M+H]⁺. ¹H NMR (400 MHz, DMSO-*d*₆) δ 8.81 – 8.69 (m, 1H), 8.60 (d, *J* = 8.0 Hz, 1H), 8.50 – 8.39 (m, 1H), 8.02 – 7.73 (m, 1H), 7.59 – 7.43 (m, 1H), 6.39 – 5.86 (m, 1H), 5.42 – 4.77 (m, 2H), 3.51 – 3.29 (m, 3H), 1.86 – 1.46 (m, 3H).

Example 98: (R)-(7-Methoxy-1H-imidazo[4,5-b]pyridin-2-yl)(5-methyl-7,8-dihydro-1,6-naphthyridin-6(5H)-yl)methanone



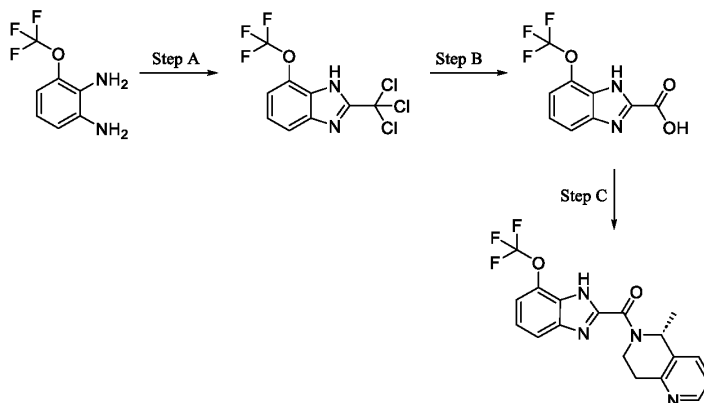
[00401] (R)-(7-Methoxy-1H-imidazo[4,5-b]pyridin-2-yl)(5-methyl-7,8-dihydro-1,6-naphthyridin-6(5H)-yl)methanone was prepared from 4,5-diamino-2-methylbenzonitrile according to the procedure of Example 89, Steps A, B, C, D, and E. LC-MS: 324.0 [M+H]⁺. ¹H NMR (400 MHz, DMSO-*d*₆) δ = 8.48 – 8.33 (m, 1H), 7.88 – 7.56 (m, 2H), 7.37 – 7.14 (m, 1H), 6.03 (d, *J* = 7.5 Hz, 1H), 5.91 – 5.61 (m, 1H), 4.91 – 4.61 (m, 1H), 3.82 (s, 3H), 3.65 (br d, *J* = 3.1 Hz, 1H), 3.01 – 2.88 (m, 2H), 1.72 – 1.49 (m, 3H).

Example 99: (R)-N,N-Dimethyl-2-(5-methyl-5,6,7,8-tetrahydro-1,6-naphthyridine-6-carbonyl)-1H-benzo[d]imidazole-7-sulfonamide



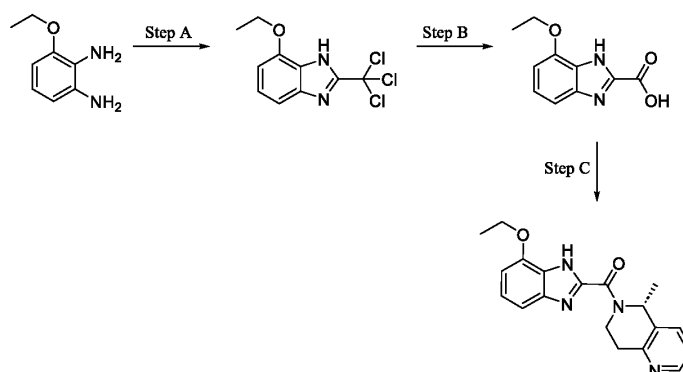
[00402] (R)-N,N-Dimethyl-2-(5-methyl-5,6,7,8-tetrahydro-1,6-naphthyridine-6-carbonyl)-1H-benzo[d]imidazole-7-sulfonamide was prepared from 2,3-diamino-N,N-dimethylbenzenesulfonamide according to the procedure of Example 30, Steps A, B, and C. LC-MS: 400.1 [M+H]⁺. ¹H NMR (400 MHz, DMSO-*d*₆) δ 8.83 – 8.24 (m, 2H), 7.98 – 7.70 (m, 3H), 7.59 – 7.45 (m, 1H), 5.99 – 5.84 (m, 1H), 4.81 (br dd, J = 5.9, 13.1 Hz, 1H), 3.79 – 3.16 (m, 3H), 2.79 (s, 6H), 1.83 – 1.51 (m, 3H).

Example 100: (R)-(5-Methyl-7,8-dihydro-1,6-naphthyridin-6(5H)-yl)(7-(trifluoromethoxy)-1H-benzo[d]imidazol-2-yl)methanone



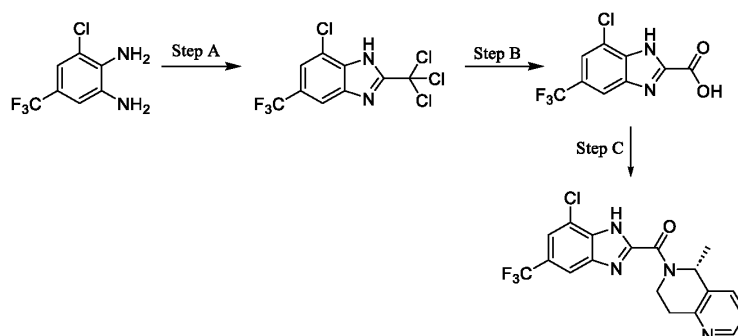
[00403] (R)-(5-Methyl-7,8-dihydro-1,6-naphthyridin-6(5H)-yl)(7-(trifluoromethoxy)-1H-benzo[d]imidazol-2-yl)methanone was prepared from 3-(trifluoromethoxy)benzene-1,2-diamine according to the procedure of Example 30, Steps A, B, and C. LC-MS: 377.0 [M+H]⁺. ¹H NMR (400 MHz, DMSO-*d*₆) δ 8.88 – 8.70 (m, 1H), 8.65 – 8.36 (m, 1H), 8.00 – 7.82 (m, 1H), 7.71 – 7.58 (m, 1H), 7.46 – 7.24 (m, 2H), 6.70 – 5.89 (m, 1H), 5.73 – 4.66 (m, 2H), 3.81 – 3.12 (m, 3H), 1.90 – 1.47 (m, 3H).

Example 101: (R)-(7-Ethoxy-1H-benzo[d]imidazol-2-yl)(5-methyl-7,8-dihydro-1,6-naphthyridin-6(5H)-yl)methanone



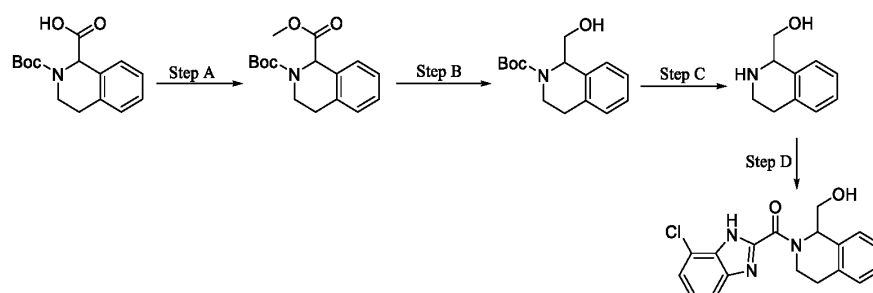
[00404] (R)-(7-Ethoxy-1H-benzo[d]imidazol-2-yl)(5-methyl-7,8-dihydro-1,6-naphthyridin-6(5H)-yl)methanone was prepared from 3-ethoxybenzene-1,2-diamine according to the procedure of Example 30, Steps A, B, and C. LC-MS: 337.1 $[M+H]^+$. 1H NMR (400 MHz, DMSO- d_6) δ 8.48 – 8.35 (m, 1H), 7.82 – 7.58 (m, 1H), 7.33 – 7.05 (m, 3H), 6.84 – 6.50 (m, 1H), 5.89 – 5.61 (m, 1H), 4.80 – 4.24 (m, 2H), 4.20 – 3.58 (m, 1H), 3.31 – 2.88 (m, 3H), 1.71 – 1.49 (m, 3H), 1.49 – 1.35 (m, 3H).

Example 102: (R)-(7-Chloro-5-(trifluoromethyl)-1H-benzo[d]imidazol-2-yl)(5-methyl-7,8-dihydro-1,6-naphthyridin-6(5H)-yl)methanone



[00405] (R)-(7-Chloro-5-(trifluoromethyl)-1H-benzo[d]imidazol-2-yl)(5-methyl-7,8-dihydro-1,6-naphthyridin-6(5H)-yl)methanone was prepared from 3-chloro-5-(trifluoromethyl)benzene-1,2-diamine according to the procedure of Example 30, Steps A, B, and C. LC-MS: 395.0 $[M+H]^+$. 1H NMR (400 MHz, DMSO- d_6) δ 8.48 – 8.35 (m, 1H), 7.95 – 7.59 (m, 3H), 7.36 – 7.20 (m, 1H), 5.85 – 5.44 (m, 1H), 4.86 – 3.36 (m, 2H), 3.21 – 2.93 (m, 2H), 1.76 – 1.53 (m, 3H).

Example 103: (7-Chloro-1H-benzo[d]imidazol-2-yl)(1-(hydroxymethyl)-3,4-dihydroisoquinolin-2(1H)-yl)methanone



[00406] Step A: To a solution of 2-(tert-butoxycarbonyl)-1,2,3,4-tetrahydroisoquinoline-1-carboxylic acid (1.00 g, 3.61 mmol) in DMF (15.0 mL) were added MeI (614 mg, 4.33 mmol) and K_2CO_3 (598 mg, 4.33 mmol) at 25 °C. The mixture was stirred at 25 °C for 2 h. The mixture was poured into water (20.0 ml) and extracted with EtOAc (20.0 ml x 3). The organic layer was washed with brine, dried over $MgSO_4$ and concentrated in vacuum to give a residue. The residue was purified by flash silica gel chromatography using a gradient of EtOAc/petroleum ether from 0/1 to 1/1 to afford 2-(tert-butyl) 1-methyl 3,4-dihydroisoquinoline-1,2(1H)-dicarboxylate. LC-MS: 192.2 $[M+H]^+$.

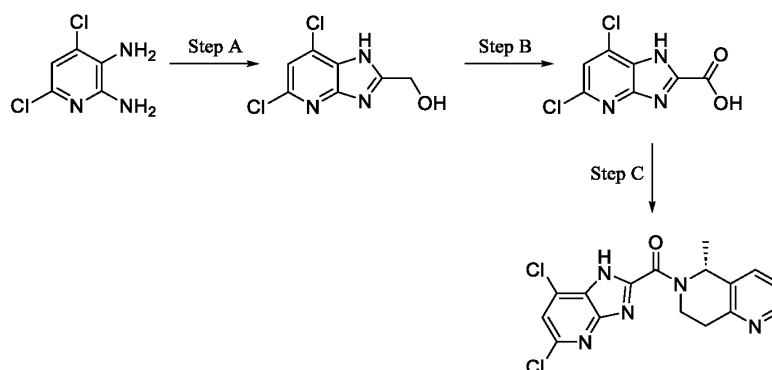
[00407] Step B: To a solution of 2-(tert-butyl) 1-methyl 3,4-dihydroisoquinoline-1,2(1H)-dicarboxylate (300 mg, 1.03 mmol) in THF (6.00 mL) was added LAH (2.5M, 0.82 mL) at 0 °C. The mixture was stirred at 25 °C for 1 h. The reaction mixture was cooled to 0 °C, quenched by addition of 0.80 mL of H_2O , followed by 0.80 mL of 10% aqueous NaOH, 2.40 mL of H_2O , after being stirred at room temperature for 5 min, then added Na_2SO_4 . The mixture was filtered through Celite pad. The filtrate was concentrated in vacuum to give a residue, which was purified by flash silica gel chromatography using a gradient of EtOAc/petroleum ether from 1/0 to 0/1 to afford tert-butyl 1-(hydroxymethyl)-3,4-dihydroisoquinoline-2(1H)-carboxylate. LC-MS: 164.2 $[M+H]^+$.

[00408] Step C: A solution of tert-butyl 1-(hydroxymethyl)-3,4-dihydroisoquinoline-2(1H)-carboxylate (100 mg, 0.380 mmol) in HCl/EtOAc (4M, 2.50 mL) was stirred at 20 °C for 1 h. The mixture was concentrated under vacuum to give (1,2,3,4-tetrahydroisoquinolin-1-yl)methanol. LC-MS: 164.2 $[M+H]^+$.

[00409] Step D: A mixture of (1,2,3,4-tetrahydroisoquinolin-1-yl)methanol (100 mg, 0.501 mmol), 7-chloro-1H-benzimidazole-2-carboxylic acid (98.5 mg, 0.501 mmol), DIEA (194 mg, 1.50 mmol) and HATU (95.2 mg, 0.250 mmol) in DMF (2.00 mL) was stirred at 20 °C for 1 h. The reaction mixture was poured into H_2O (5.00 mL) and extracted with DCM (5.00 mL x 4). The combined organic layers were dried over Na_2SO_4 , filtered, and concentrated under vacuum to give a residue which was purified by preparative HPLC (Phenomenex Luna C18 column (100 ×

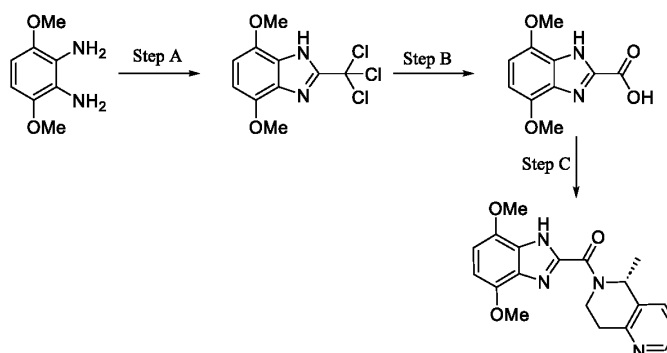
40 mm, 5 (m); flow rate: 25 mL/min; gradient: 25% – 55% B over 8 min; mobile phase A: 0.1% aqueous HCl, mobile phase B: acetonitrile) to afford (7-chloro-1H-benzo[d]imidazol-2-yl)(1-(hydroxymethyl)-3,4-dihydroisoquinolin-2(1H)-yl)methanone. LC-MS: 342.1 [M+H]⁺. ¹H NMR (400 MHz, DMSO-*d*₆) δ 7.58 – 7.50 (m, 1H), 7.45 – 7.14 (m, 6H), 6.46 – 5.62 (m, 1H), 5.47 – 4.53 (m, 1H), 3.89 – 3.80 (m, 1H), 3.74 – 3.57 (m, 1H), 3.37 – 3.29 (m, 1H), 3.08 – 2.84 (m, 2H).

Example 104: (R)-(5,7-Dichloro-1H-imidazo[4,5-b]pyridin-2-yl)(5-methyl-7,8-dihydro-1,6-naphthyridin-6(5H)-yl)methanone



[00410] (R)-(5,7-Dichloro-1H-imidazo[4,5-b]pyridin-2-yl)(5-methyl-7,8-dihydro-1,6-naphthyridin-6(5H)-yl)methanone was prepared from 4,6-dichloropyridine-2,3-diamine according to the procedure of Example 35, Steps A, B, and C. LC-MS: 362.2 [M+H]⁺. ¹H NMR (400 MHz, DMSO-*d*₆) δ 8.77 – 8.60 (m, 1H), 8.45 – 8.11 (m, 1H), 7.82 – 7.57 (m, 2H), 6.45 – 5.71 (m, 1H), 5.46 – 4.62 (m, 1H), 3.78 – 3.64 (m, 1H), 3.42 (br s, 1H), 3.22 – 3.08 (m, 1H), 1.74 (d, *J* = 6.8 Hz, 1H), 1.60 (d, *J* = 6.8 Hz, 2H).

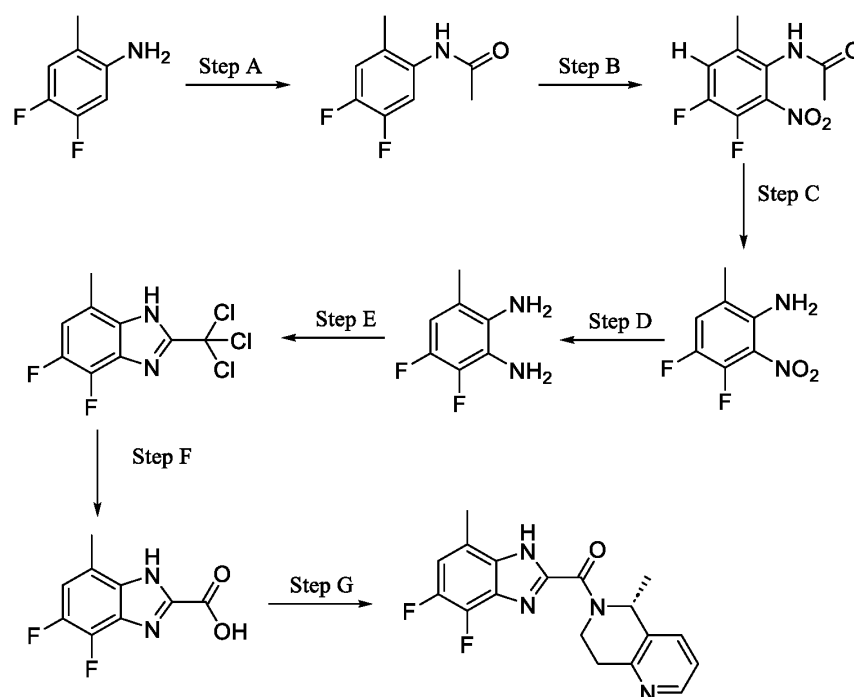
Example 105: (R)-(4,7-Dimethoxy-1H-benzo[d]imidazol-2-yl)(5-methyl-7,8-dihydro-1,6-naphthyridin-6(5H)-yl)methanone



[00411] (R)-(4,7-Dimethoxy-1H-benzo[d]imidazol-2-yl)(5-methyl-7,8-dihydro-1,6-naphthyridin-6(5H)-yl)methanone was prepared from 3,6-dimethoxybenzene-1,2-diamine

according to the procedure of Example 30, Steps A, B, and C. LC-MS: 353.1 $[M+H]^+$. 1H NMR (400 MHz, DMSO- d_6) δ 8.80 – 8.68 (m, 1H), 8.60 – 8.40 (m, 1H), 7.97 – 7.78 (m, 1H), 6.71 (s, 2H), 5.90 (q, J = 6.5 Hz, 1H), 5.40 (br dd, J = 4.9, 13.6 Hz, 1H), 4.78 (br dd, J = 5.4, 13.3 Hz, 1H), 3.89 (s, 6H), 3.26 (br d, J = 16.3 Hz, 2H), 1.76 – 1.54 (m, 3H).

Example 106: (R)-(4,5-Difluoro-7-methyl-1H-benzo[d]imidazol-2-yl)(5-methyl-7,8-dihydro-1,6-naphthyridin-6(5H)-yl)methanone



[00412] Step A: A mixture of 4,5-difluoro-2-methyl-aniline (2.00 g, 14.0 mmol), TEA (4.24 g, 42.0 mmol) and Ac₂O (1.71 g, 17.0 mmol) in DCM (80.0 mL) was stirred at 20 °C for 12 h. The reaction mixture was poured into H₂O (50.0 mL) and extracted with DCM (50.0 mL x 3). The combined organic layers were dried over Na₂SO₄, filtered, and concentrated under vacuum to give a residue which was purified by flash silica gel chromatography using a gradient of EtOAc/petroleum ether from 1/100 to 1/3 to afford N-(4,5-difluoro-2-methylphenyl)acetamide. LC-MS: 186.2 $[M+H]^+$.

[00413] Step B: H₂SO₄ (22.5 mL) was cooled to -10 °C and N-(4,5-difluoro-2-methylphenyl)acetamide (1.13 g, 6.10 mmol) was slowly added. Then a mixture of HNO₃ (19.0 g, 305 mmol) and H₂SO₄ (13.0 mL) was added. The mixture was stirred for 0.5 hr at 0 °C, then stirred at 25 °C for 1 h. The reaction mixture is then poured into ice water (200 ml) and adjusted pH 7 by using NaOH (2M aqueous), and then extracted with EtOAc (50.0 mL x 3). The combined organic layers were dried over Na₂SO₄, filtered and concentrated under reduced pressure to give

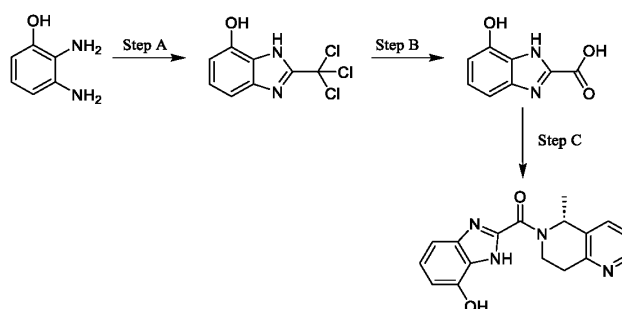
a residue, which was purified by flash silica gel chromatography using a gradient of EtOAc/petroleum ether from 1/100 to 1/3 to afford N-(3,4-difluoro-6-methyl-2-nitro-phenyl)acetamide. LC-MS: 231.2 [M+H]⁺.

[00414] Step C: A mixture of N-(3,4-difluoro-6-methyl-2-nitro-phenyl)acetamide (500 mg, 2.17 mmol) and HCl (2M, 12.5 mL) in MeOH (50.0 mL) was stirred at 80 °C for 8 h. The reaction mixture was poured into H₂O (50.0 mL) and extracted with DCM (50.0 mL x 3). The combined organic layers were dried over Na₂SO₄, filtered, and concentrated under vacuum to give a residue which was purified by flash silica gel chromatography using a gradient of EtOAc/petroleum ether from 1/100 to 1/3 to afford 3,4-difluoro-6-methyl-2-nitroaniline. LC-MS: 189.2 [M+H]⁺.

[00415] Step D: A solution of 3,4-difluoro-6-methyl-2-nitroaniline (250 mg, 1.33 mmol) and Pd/C (250 mg, 10% purity) in EtOAc (20.0 mL) was degassed and purged with H₂ for three times. The mixture was stirred at 20 °C for 1 h under H₂ (15 psi) atmosphere. The mixture was filtered through Celite pad, filtered, and concentrated under vacuum to give 3,4-difluoro-6-methylbenzene-1,2-diamine. LC-MS: 159.2 [M+H]⁺.

[00416] Steps E, F, and G: (R)-(4,5-Difluoro-7-methyl-1H-benzo[d]imidazol-2-yl)(5-methyl-7,8-dihydro-1,6-naphthyridin-6(5H)-yl)methanone was prepared from 3,4-difluoro-6-methylbenzene-1,2-diamine according to the procedure of Example 30, Steps A, B, and C. LC-MS: 343.0 [M+H]⁺. ¹H NMR (400 MHz, DMSO-*d*₆) δ 8.79 – 8.65 (m, 1H), 8.57 – 8.42 (m, 1H), 8.00 – 7.74 (m, 1H), 7.30 – 7.10 (m, 1H), 6.58 – 5.81 (m, 1H), 5.48 (br dd, *J* = 5.5, 13.8 Hz, 1H), 3.69 (br d, *J* = 10.4 Hz, 1H), 3.44 – 3.18 (m, 2H), 2.52 (br s, 3H), 1.82 – 1.57 (m, 3H).

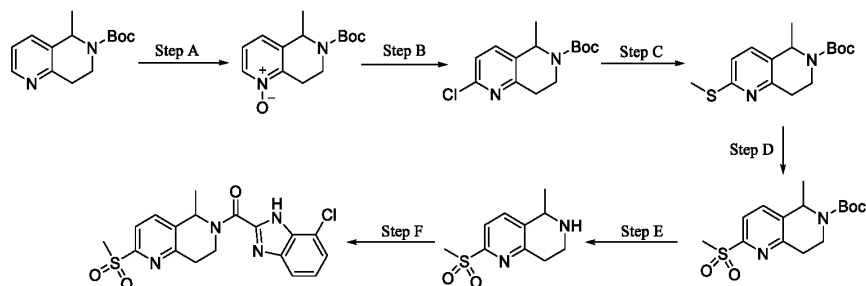
Example 107: (R)-(7-Hydroxy-1H-benzo[d]imidazol-2-yl)(5-methyl-7,8-dihydro-1,6-naphthyridin-6(5H)-yl)methanone



[00417] (R)-(7-Hydroxy-1H-benzo[d]imidazol-2-yl)(5-methyl-7,8-dihydro-1,6-naphthyridin-6(5H)-yl)methanone was prepared from 2,3-diaminophenol according to the procedure of Example 30, Steps A, B, and C. LC-MS: 309.1 [M+H]⁺. ¹H NMR (400 MHz, DMSO-*d*₆) δ 13.19

– 12.67 (m, 1H), 10.04 – 9.64 (m, 1H), 8.41 (br d, $J = 4.4$ Hz, 1H), 7.89 – 7.63 (m, 1H), 7.34 – 6.47 (m, 4H), 6.04 – 5.42 (m, 1H), 4.87 – 3.58 (m, 1H), 3.28 – 2.73 (m, 3H), 1.69 – 1.47 (m, 3H).

Example 108: (7-Chloro-1H-benzo[d]imidazol-2-yl)(5-methyl-2-(methylsulfonyl)-7,8-dihydro-1,6-naphthyridin-6(5H)-yl)methanone



[00418] Step A: To a solution of *tert*-butyl 5-methyl-7,8-dihydro-5H-1,6-naphthyridine-6-carboxylate (2.00 g, 8.05 mmol) in DCM (20.0 mL) was added *m*-CPBA (3.47 g, 16.1 mmol, 80% purity). The mixture was stirred at 25 °C for 2 h. The reaction mixture was concentrated, diluted with saturated aqueous NaHCO₃ (10.0 mL) and extracted with EtOAc (10.0 mL x 3). The combined organic layers were dried over Na₂SO₄, filtered and concentrated under reduced pressure to give a residue which was purified by flash silica gel chromatography using a gradient of MeOH/DCM from 7/93 to 3/97 to give *tert*-butyl 5-methyl-1-oxido-7,8-dihydro-5H-1,6-naphthyridin-1-ium-6-carboxylate. LC-MS: 265.2 [M+H]⁺.

[00419] Step B: To a solution of 6-(*tert*-butoxycarbonyl)-5-methyl-5,6,7,8-tetrahydro-1,6-naphthyridine 1-oxide (50.0 mg, 0.189 mmol) in DMF (2.00 mL) was added (COCl)₂ (1.00 g, 11.0 mmol). The mixture was stirred at 50 °C for 4 h. The reaction mixture was concentrated, diluted with H₂O (20.0 mL) and extracted with EtOAc (30.0 mL x 3). The combined organic layers were dried over Na₂SO₄, filtered and concentrated under reduced pressure to give a residue which was purified by flash silica gel chromatography using a gradient of EtOAc/petroleum ether from 1/6 to 1/4 to give *tert*-butyl 2-chloro-5-methyl-7,8-dihydro-1,6-naphthyridine-6(5H)-carboxylate. LC-MS: 283.2 [M+H]⁺.

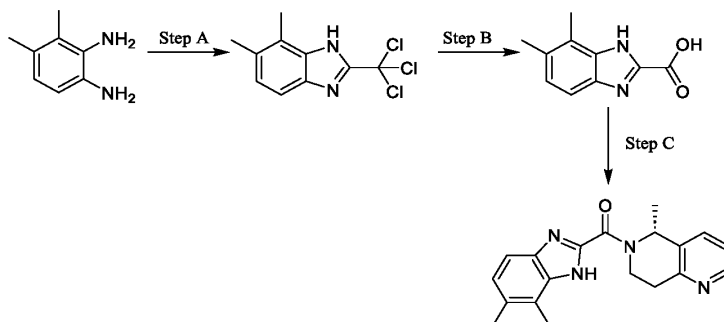
[00420] Step C: To a solution of *tert*-butyl 2-chloro-5-methyl-7,8-dihydro-1,6-naphthyridine-6(5H)-carboxylate (120 mg, 0.424 mmol) in THF (3.00 mL) was added Cs₂CO₃ (277 mg, 0.849 mmol) and NaSMe (480 mg, 7.00 mmol) and MeONa (220 mg, 3.00 mmol). The mixture was stirred at 80 °C for 12 h. The reaction mixture was quenched by NaClO (10.0 mL) and extracted with EtOAc (10.0 mL x 3). The combined organic layers were dried over Na₂SO₄, filtered and concentrated under reduced pressure to give a residue which was purified by preparative TLC (SiO₂, Petroleum ether/EtOAc=2/1) to give *tert*-butyl 5-methyl-2-(methylthio)-7,8-dihydro-1,6-naphthyridine-6(5H)-carboxylate. LC-MS: 295.2 [M+H]⁺.

[00421] Step D: To a solution of *tert*-butyl 5-methyl-2-(methylthio)-7,8-dihydro-1,6-naphthyridine-6(5*H*)-carboxylate (30.0 mg, 0.102 mmol) in DCM (1.00 mL) was added *m*-CPBA (41.0 mg, 0.204 mmol, 85% purity). The mixture was stirred at 25 °C for 4 h. The residue was diluted with Na₂SO₃ (20 mL) and extracted with DCM (20.0 mL x 3). The combined organic layers were dried over Na₂SO₄, filtered and concentrated under reduced pressure to give a residue which was purified by preparative TLC (SiO₂, Petroleum ether/EtOAc= 1/1) to afford *tert*-butyl 5-methyl-2-(methylsulfonyl)-7,8-dihydro-1,6-naphthyridine-6(5*H*)-carboxylate. LC-MS: 372.2 [M+H]⁺.

[00422] Step E: A solution of *tert*-butyl 5-methyl-2-(methylsulfonyl)-7,8-dihydro-1,6-naphthyridine-6(5*H*)-carboxylate (20.0 mg, 0.061 mmol) in 4M HCl/EtOAc (3.00 mL) was stirred at 25 °C for 0.5 h. The reaction mixture was concentrated under reduced pressure to give 5-methyl-2-(methylsulfonyl)-5,6,7,8-tetrahydro-1,6-naphthyridine. LC-MS: 227.2 [M+H]⁺.

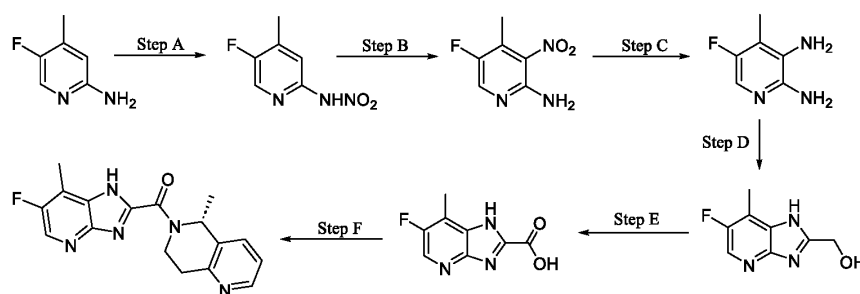
[00423] Step F: To a solution of 7-chloro-1*H*-benzo[*d*]imidazole-2-carboxylic acid (22.0 mg, 0.110 mmol) in DCM (0.50 mL) was added TEA (34.0 mg, 0.331 mmol) and BOP-Cl (42.0 mg, 0.166 mmol), after stirred for 1 h, 5-methyl-2-(methylsulfonyl)-5,6,7,8-tetrahydro-1,6-naphthyridine (25.0 mg, 0.110 mmol) was added. The mixture was stirred at 25 °C for 1 h. The mixture was concentrated under reduced pressure to give a residue which was purified by prep-HPLC (column: Phenomenex luna C18 100 x 40mm x 5 μm; mobile phase: [H₂O (0.04% HCl)-ACN]; gradient: 25%-55% B over 8.0 min) to afford (7-chloro-1*H*-benzo[*d*]imidazol-2-yl)(5-methyl-2-(methylsulfonyl)-7,8-dihydro-1,6-naphthyridin-6(5*H*)-yl)methanone. LC-MS: 405.1 [M+H]⁺. ¹H NMR (400 MHz, DMSO-*d*₆) δ 8.22 – 8.01 (m, 1H), 7.96 – 7.84 (m, 1H), 7.56 (br d, *J* = 7.9 Hz, 1H), 7.40 – 7.36 (m, 1H), 7.35 – 7.29 (m, 1H), 5.93 – 5.84 (m, 0.6H), 5.79 – 5.58 (m, 1H), 4.76 (br dd, *J* = 2.9, 11.5 Hz, 0.4H), 3.82 – 3.75 (m, 1H), 3.49 – 3.44 (m, 1H), 3.29 – 3.24 (m, 3H), 3.14 – 3.05 (m, 1H), 1.79 – 1.55 (m, 3H).

Example 109: (*R*)-(6,7-Dimethyl-1*H*-benzo[*d*]imidazol-2-yl)(5-methyl-7,8-dihydro-1,6-naphthyridin-6(5*H*)-yl)methanone



[00424] Steps A, B, and C: (R)-(6,7-Dimethyl-1H-benzo[d]imidazol-2-yl)(5-methyl-7,8-dihydro-1,6-naphthyridin-6(5H)-yl)methanone was prepared from 3,4-dimethylbenzene-1,2-diamine according to the procedure of Example 30, Steps A, B, and C. LC-MS: 321.1 [M+H]⁺. ¹H NMR (400 MHz, DMSO-*d*₆) δ 8.80 – 8.71 (m, 1H), 8.61 (d, *J* = 7.7 Hz, 1H), 7.97 – 7.83 (m, 1H), 7.43 – 7.34 (m, 1H), 7.22 – 7.12 (m, 1H), 5.92 – 5.42 (m, 2H), 3.83 – 3.59 (m, 1H), 3.36 (br d, *J* = 14.9 Hz, 2H), 2.49 (br s, 3H), 2.37 – 2.29 (m, 3H), 1.77 – 1.58 (m, 3H).

Example 110: (R)-(6-Fluoro-7-methyl-1H-imidazo[4,5-b]pyridin-2-yl)(5-methyl-7,8-dihydro-1,6-naphthyridin-6(5H)-yl)methanone



[00425] Step A: To a solution of 5-fluoro-4-methylpyridin-2-amine (2.00 g, 16.0 mmol) in H₂SO₄ (10.0 mL) was added HNO₃ (5.00 g, 79.0 mmol). The mixture was stirred at 0 °C for 1 h. It was poured into water until some solid appeared. The precipitate was collected by filtration and dried by concentration to give N-(5-fluoro-4-methylpyridin-2-yl)nitramide. LC-MS: 172.1 [M+H]⁺.

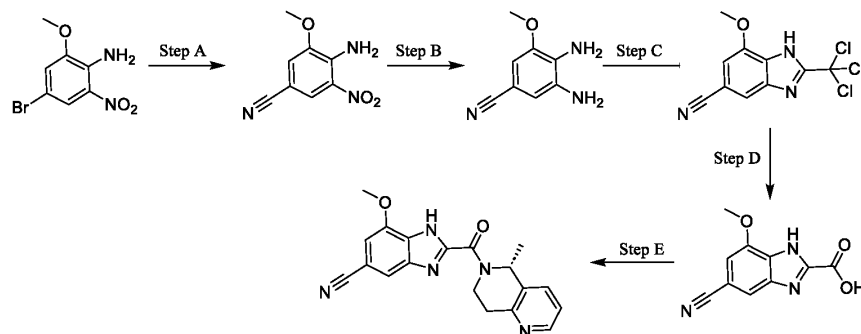
[00426] Step B: A solution of N-(5-fluoro-4-methyl-2-pyridyl)nitramide (2.00 g, 9.00 mmol) in H₂SO₄ (5.00 mL) was stirred at 25 °C for 3 h. The reaction mixture was quenched by saturated Na₂CO₃ aqueous (30.0 mL) at 0 °C, and then extracted with EtOAc (50.0 mL x 3). The combined organic layers were dried over Na₂SO₄, filtered and concentrated under reduced pressure to give 5-fluoro-4-methyl-3-nitropyridin-2-amine. LC-MS: 172.1 [M+H]⁺.

[00427] Step C: To a solution of 5-fluoro-4-methyl-3-nitropyridin-2-amine (320 mg, 2.00 mmol) in EtOH (40.0 mL) was added SnCl₂·2H₂O (4.00 g, 18.0 mmol). The mixture was stirred at 70 °C for 2 h. The reaction mixture was quenched by Na₂CO₃ (aq., 100 mL) at 0 °C, and extracted with EtOAc (100 mL x 3). The combined organic layers were dried over Na₂SO₄, filtered and concentrated under reduced pressure to give 5-fluoro-4-methylpyridine-2,3-diamine. LC-MS: 142.1 [M+H]⁺.

[00428] Steps D, E, and F: (R)-(6-Fluoro-7-methyl-1H-imidazo[4,5-b]pyridin-2-yl)(5-methyl-7,8-dihydro-1,6-naphthyridin-6(5H)-yl)methanone was prepared from 5-fluoro-4-methylpyridine-2,3-diamine according to the procedure of Example 35, Steps A, B, and C. LC-MS:

326.1 [M+H]⁺. ¹H NMR (400 MHz, DMSO-*d*₆) δ 8.64 (br d, *J* = 5.1 Hz, 1H), 8.42 – 8.39 (m, 1H), 8.36 – 8.29 (m, 1H), 7.73 (br s, 1H), 6.63 – 5.86 (m, 1H), 5.59 – 5.35 (m, 1H), 3.79 – 3.66 (m, 1H), 3.40 – 3.22 (m, 2H), 2.58 (d, *J* = 1.6 Hz, 3H), 1.66 (br d, *J* = 2.4 Hz, 3H).

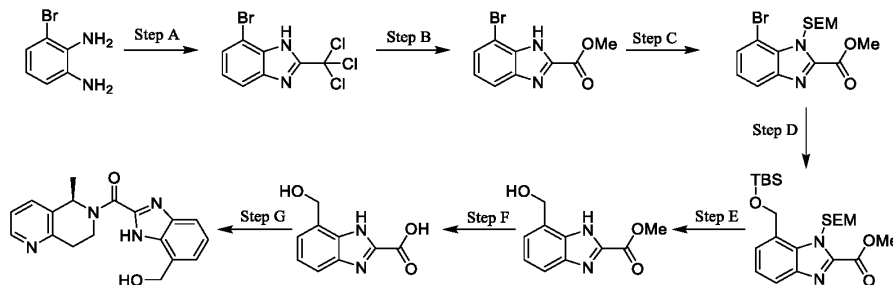
Example 111: (R)-7-Methoxy-2-(5-methyl-5,6,7,8-tetrahydro-1,6-naphthyridine-6-carbonyl)-1H-benzo[d]imidazole-5-carbonitrile



[00429] Step A: To a solution of 4-bromo-2-methoxy-6-nitro-aniline (4.00 g, 16.2 mmol) in DMF (16.0 mL) and pyridine (2.00 mL) was added CuCN (4.35 g, 48.6 mmol). The mixture was stirred at 160 °C for 6 h. The reaction mixture was poured into H₂O (30.0 mL) and the resulting mixture was filtered and the filter cake was dried under vacuum to give 4-amino-3-methoxy-5-nitro-benzonitrile. LC-MS: 192.6 [M+H]⁺.

[00430] Steps B, C, D, and E: (R)-7-Methoxy-2-(5-methyl-5,6,7,8-tetrahydro-1,6-naphthyridine-6-carbonyl)-1H-benzo[d]imidazole-5-carbonitrile was prepared from 4-amino-3-methoxy-5-nitro-benzonitrile according to the procedure of Example 84, Steps A, B, C, and D. LC-MS: 218.2 [M+H]⁺. ¹H NMR (400 MHz, CDCl₃) δ 8.76 – 8.51 (m, 1H), 8.40 – 8.13 (m, 1H), 7.82 – 7.38 (m, 2H), 6.96 (br d, *J* = 3.4 Hz, 1H), 6.57 – 5.90 (m, 1H), 5.22 – 4.12 (m, 1H), 4.05 (d, *J* = 2.6 Hz, 3H), 3.98 – 3.81 (m, 1H), 3.78 – 3.56 (m, 1H), 3.54 – 3.27 (m, 1H), 1.87 – 1.68 (m, 3H).

Example 112: (R)-(7-(Hydroxymethyl)-1H-benzo[d]imidazol-2-yl)(5-methyl-7,8-dihydro-1,6-naphthyridin-6(5H)-yl)methanone



[00431] Step A: To a solution of 3-bromobenzene-1,2-diamine (3.00 g, 16.0 mmol) in AcOH (30.0 mL) was added methyl 2,2,2-trichloroethanimidate (5.66 g, 32.1 mmol, 3.97 mL). The mixture was stirred at 0 °C for 2 h. The reaction mixture was treated with H₂O solution until some solid appeared. The mixture was filtered and the cake was dried in vacuum to give 7-bromo-2-(trichloromethyl)-1H-benzo[d]imidazole. LC-MS: 312.8 [M+H]⁺.

[00432] Step B: A solution of Na₂CO₃ (1.69 g, 15.9 mmol) in H₂O (10.0 mL) was added to a solution of 7-bromo-2-(trichloromethyl)-1H-benzimidazole (5.00 g, 15.9 mmol) in MeOH (60.0 mL). The mixture was stirred at 80 °C for 12 h. The reaction mixture was concentrated to give a residue. The residue was diluted with H₂O (30.0 mL) and extracted with EtOAc (30.0 mL × 3). The combined organic layers were dried over Na₂SO₄, filtered and concentrated under vacuum to give a residue, which was purified by flash silica gel chromatography using a gradient of EtOAc/petroleum ether from 0/1 to 1/1 to afford methyl 7-bromo-1H-benzo[d]imidazole-2-carboxylate. LC-MS: 254.8 [M+H]⁺.

[00433] Step C: To a solution of methyl 7-bromo-1H-benzimidazole-2-carboxylate (2.00 g, 7.84 mmol) in THF (30.0 mL) was added NaH (376 mg, 9.41 mmol, 60% purity) at 0 °C and the resulting mixture was stirred at 0 °C for 0.5 h. Then 2-(chloromethoxy)ethyl-trimethyl-silane (1.96 g, 11.8 mmol, 2.08 mL) was added and the resulting mixture was stirred at 20 °C for 2 h. The residue was diluted with NH₄Cl (30.0 mL) and extracted with EtOAc (20.0 mL × 3). The combined organic layers were dried over Na₂SO₄, filtered, and concentrated under vacuum to give a residue, which was purified by flash silica gel chromatography using a gradient of EtOAc/petroleum ether from 0/1 to 3/1 to afford methyl 7-bromo-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-benzo[d]imidazole-2-carboxylate. LC-MS: 385.1 [M+H]⁺.

[00434] Step D: To a solution of methyl 7-bromo-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-benzo[d]imidazole-2-carboxylate (1.00 g, 2.56 mmol) in dioxane (15.0 mL) was added tert-butyl-dimethyl-(tributylstannylmethoxy)silane (2.26 g, 5.19 mmol) and Pd(PPh₃)₂Cl₂ (182 mg, 0.256 mmol). The mixture was stirred at 60 °C for 12 h under N₂. The reaction mixture was concentrated to give a residue. The residue was dissolved in MeOH (5.00 mL) and purified by prep-HPLC (Phenomenex Gemini C18 100×30mm×10um; flow rate: gradient:30%-60% B over 8.0 min mobile phase 10 mM aqueous NH₄HCO₃) to afford methyl 7-(((tert-butyl)dimethylsilyl)oxy)methyl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-benzo[d]imidazole-2-carboxylate. LC-MS: 451.4 [M+H]⁺.

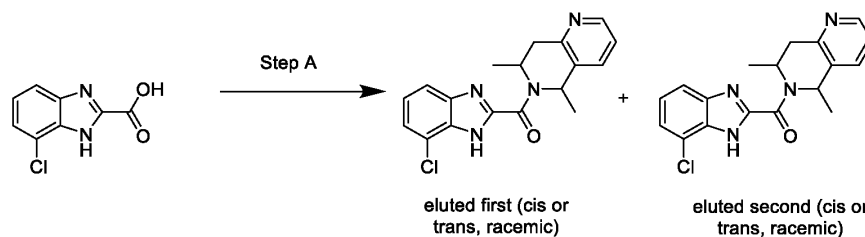
[00435] Step E: A solution of methyl 7-(((tert-butyl)dimethylsilyl)oxy)methyl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-benzo[d]imidazole-2-carboxylate (430 mg, 0.954 mmol) in TFA (7.68 g, 67.3 mmol, 5.00 mL) was stirred at 50 °C for 2 h. The reaction mixture was

concentrated to give methyl 7-(hydroxymethyl)-1H-benzimidazole-2-carboxylate, which was used in next step directly. LC-MS: 207.2 [M+H]⁺.

[00436] Step F: To a solution of methyl 7-(hydroxymethyl)-1H-benzimidazole-2-carboxylate (200 mg, 0.969 mmol) in MeOH (3.00 mL) was added NaOH (2M, 10.0 mL) at 0 °C. The mixture was stirred at 0 °C for 2 h. The reaction mixture was concentrated to give a residue. The residue was dissolved in MeOH (5.00 mL) and was purified by prep-HPLC (column: Phenomenex luna C18 100 × 40mm × 5 um; mobile phase: [H₂O (0.1% TFA)-ACN]; gradient: 1%-20% B over 8.0 min) to afford 7-(hydroxymethyl)-1H-benzimidazole-2-carboxylic acid. LC-MS: 193.1 [M+H]⁺.

[00437] Step G: To a solution of 7-(hydroxymethyl)-1H-benzimidazole-2-carboxylic acid (60.0 mg, 0.312 mmol) in DCM (1.00 mL) was added TEA (94.8 mg, 0.936 mmol) and BOP-Cl (119 mg, 0.468 mmol) at 0 °C and the resulting mixture was stirred at 0 °C for 1 h. (5R)-5-Methyl-5,6,7,8-tetrahydro-1,6-naphthyridine (46.3 mg, 0.312 mmol) was added and the resulting mixture was stirred at 20 °C for 2 h. The residue was dissolved in MeOH (5.00 mL) and was purified by prep-HPLC (column: Waters Xbridge BEH C18 100*30mm*10um; mobile phase: [H₂O (10mM NH₄HCO₃)-ACN]; gradient: 20%-50% B over 8.0 min). The relevant fractions were lyophilized to afford (R)-(7-(hydroxymethyl)-1H-benzo[d]imidazol-2-yl)(5-methyl-7,8-dihydro-1,6-naphthyridin-6(5H)-yl)methanone. LC-MS: 323.1 [M+H]⁺. ¹H NMR (400 MHz, DMSO-*d*₆) δ 8.58 - 8.34 (m, 1H), 7.74 (br d, *J* = 7.9 Hz, 1H), 7.65 - 7.52 (m, 1H), 7.59 (br d, *J* = 1.0 Hz, 1H), 7.48 - 7.29 (m, 3H), 6.73 - 5.77 (m, 1H), 5.75 - 5.20 (m, 1H), 4.96 (br s, 2H), 3.87 - 3.47 (m, 1H), 3.33 - 2.91 (m, 2H), 1.80 - 1.42 (m, 3H).

Examples 113A and 113B: cis or trans-(7-Chloro-1H-benzo[d]imidazol-2-yl)(1,3-dimethyl-3,4-dihydroisoquinolin-2(1H)-yl)methanone and trans or cis-(7-Chloro-1H-benzo[d]imidazol-2-yl)((1S,3S)-1,3-dimethyl-3,4-dihydroisoquinolin-2(1H)-yl)methanone

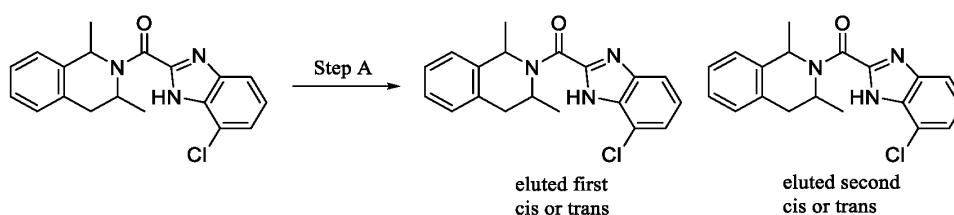


[00438] Step A: A mixture of 1,3-dimethyl-1,2,3,4-tetrahydroisoquinoline (30.0 mg, 0.186 mmol), 7-chloro-1H-benzo[d]imidazole-2-carboxylic acid (36.6 mg, 0.186 mmol), DIEA (72.1 mg, 0.558 mmol) and HATU (35.4 mg, 0.093 mmol) in DMF (1.00 mL) was stirred at 20 °C for 1 h. The reaction mixture was poured into H₂O (1.00 mL) and extracted with DCM (1.00 mL x 4). The combined organic layers were dried over Na₂SO₄, filtered, and concentrated under

vacuum to give a residue which was purified by preparative HPLC (Phenomenex Luna C18 column (100 × 40 mm, 5 μm); flow rate: 25 mL/min; gradient: 45% – 75% B over 8 min; mobile phase A: 10 mM aqueous NH₄HCO₃, mobile phase B: acetonitrile) to afford cis or trans-(7-chloro-1H-benzo[d]imidazol-2-yl)(1,3-dimethyl-3,4-dihydroisoquinolin-2(1H)-yl)methanone (first eluent) and trans or cis-(7-chloro-1H-benzo[d]imidazol-2-yl)((1S,3S)-1,3-dimethyl-3,4-dihydroisoquinolin-2(1H)-yl)methanone (second eluent).

[00439] First eluted compound (**Example 113A**): LC-MS: 340.2 [M+H]⁺. ¹H NMR (400 MHz, CDCl₃) δ 7.77 – 7.58 (m, 1H), 7.29 (br s, 3H), 7.26 – 7.16 (m, 3H), 7.11 – 6.28 (m, 1H), 5.79 – 4.90 (m, 1H), 3.54 – 3.14 (m, 1H), 2.99 – 2.72 (m, 1H), 1.75 (br s, 1H), 1.53 (br s, 2H), 1.11 – 0.98 (m, 3H). Second eluted compound (**Example 113B**): LC-MS: 340.1 [M+H]⁺. ¹H NMR (400 MHz, CDCl₃) δ 7.80 – 7.60 (m, 1H), 7.38 (s, 3H), 7.25 – 7.12 (m, 3H), 7.03 – 6.08 (m, 1H), 5.75 – 4.90 (m, 1H), 3.55 – 3.10 (m, 1H), 3.01 – 2.66 (m, 1H), 1.82 (br d, *J* = 6.5 Hz, 1H), 1.71 (br d, *J* = 6.0 Hz, 2H), 1.46 (br dd, *J* = 6.0, 14.3 Hz, 3H). The absolute stereochemistry for the first and second eluted compounds was not determined.

Examples 113C and 113D: cis- or trans-(7-Chloro-1H-benzo[d]imidazol-2-yl)(1,3-dimethyl-3,4-dihydroisoquinolin-2(1H)-yl)methanone and cis or trans-(7-Chloro-1H-benzo[d]imidazol-2-yl)(1,3-dimethyl-3,4-dihydroisoquinolin-2(1H)-yl)methanone

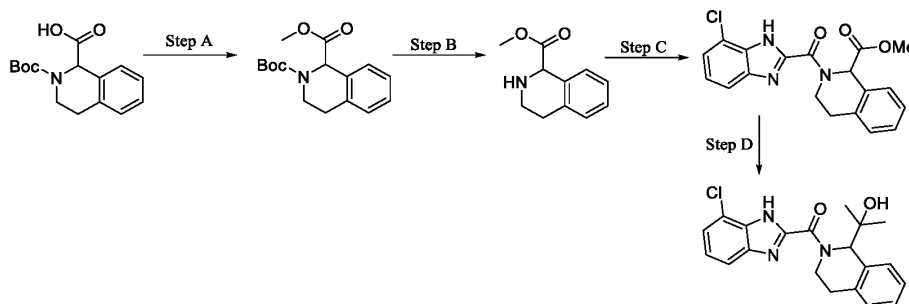


[00440] **Step A:** cis- or trans-(7-Chloro-1H-benzo[d]imidazol-2-yl)(1,3-dimethyl-3,4-dihydroisoquinolin-2(1H)-yl)methanone (16.0 mg, 0.471 mmol) was further separated by SFC separation (Phenomenex-CHIRALPAK IG (250 × 30 mm, 10 μm); flow rate: 30 mL/min; gradient: 45% B over 14 min; mobile phase A: heptane, mobile phase B: EtOH(0.1% NH₃H₂O) to afford (7-chloro-1H-benzo[d]imidazol-2-yl)((1R,3S)-1,3-dimethyl-3,4-dihydroisoquinolin-2(1H)-yl)methanone (first eluent) and (7-chloro-1H-benzo[d]imidazol-2-yl)((1S,3R)-1,3-dimethyl-3,4-dihydroisoquinolin-2(1H)-yl)methanone (second eluent).

[00441] First eluted compound (**Example 113C**): LC-MS: 340.1 [M+H]⁺. ¹H NMR (400 MHz, CDCl₃) δ 7.66 (br d, *J* = 6.9 Hz, 1H), 7.40 – 7.29 (m, 3H), 7.25 – 7.13 (m, 3H), 6.99 – 6.50 (m, 1H), 5.76 – 5.00 (m, 1H), 3.34 – 3.10 (m, 1H), 3.00 – 2.75 (m, 1H), 1.82 (br d, *J* = 6.9 Hz, 1H), 1.74 (d, *J* = 6.9 Hz, 2H), 1.47 (br dd, *J* = 6.7, 14.1 Hz, 3H). Second eluted compound (**Example 113D**): LC-MS: 340.1 [M+H]⁺. ¹H NMR (400 MHz, CDCl₃) δ 7.73 – 7.57 (m, 1H), 7.41 – 7.27

(m, 3H), 7.26 – 7.11 (m, 3H), 7.03 – 6.44 (m, 1H), 5.79 – 4.96 (m, 1H), 3.33 – 3.10 (m, 1H), 2.99 – 2.76 (m, 1H), 1.82 (br d, $J=6.9$ Hz, 1H), 1.74 (br d, $J=6.9$ Hz, 2H), 1.47 (br dd, $J=6.6$, 13.8 Hz, 3H).

Example 114: (7-Chloro-1H-benzo[d]imidazol-2-yl)(1-(2-hydroxypropan-2-yl)-3,4-dihydroisoquinolin-2(1H)-yl)methanone



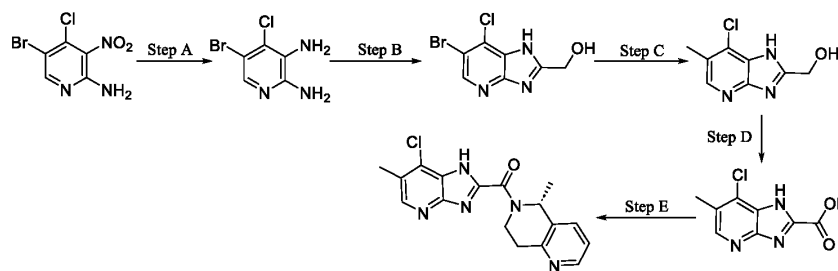
[00442] Step A: To a solution of 2-tert-butoxycarbonyl-3,4-dihydro-1H-isoquinoline-1-carboxylic acid (1.00 g, 3.61 mmol) in DMF (15.0 mL) were added K_2CO_3 (598 mg, 4.33 mmol) and MeI (614 mg, 4.33 mmol) at 25 °C. The mixture was stirred at 25 °C for 2 h. The reaction mixture was poured into H_2O (30.0 mL) and extracted with EtOAc (30.0 mL x 3). The combined organic layers were dried over Na_2SO_4 , filtered, and concentrated under vacuum to give a residue which was purified by flash silica gel chromatography using a gradient of EtOAc/petroleum ether from 0/1 to 1/0 to afford 2-(tert-butyl) 1-methyl 3,4-dihydroisoquinoline-1,2(1H)-dicarboxylate. LC-MS: 192.2 $[M+H]^+$.

[00443] Step B: A solution of 2-(tert-butyl) 1-methyl 3,4-dihydroisoquinoline-1,2(1H)-dicarboxylate (300 mg, 1.03 mmol) in HCl/EtOAc (4M, 3.00 mL) was stirred at 25 °C for 1 h. The mixture was concentrated under vacuum to give methyl 1,2,3,4-tetrahydroisoquinoline-1-carboxylate. LC-MS: 192.5 $[M+H]^+$.

[00444] Step C: A mixture of methyl 1,2,3,4-tetrahydroisoquinoline-1-carboxylate (300 mg, 1.57 mmol), 7-chloro-1H-benzimidazole-2-carboxylic acid (308 mg, 1.57 mmol), DIEA (608 mg, 4.71 mmol) and HATU (298 mg, 0.784 mmol) in DMF (5.00 mL) was stirred at 20 °C for 1 h. The reaction mixture was poured into H_2O (5.00 mL) and extracted with DCM (5.00 mL x 4). The combined organic layers were dried over Na_2SO_4 , filtered, and concentrated under vacuum to give a residue which was purified by flash silica gel chromatography using a gradient of EtOAc/petroleum ether from 0/1 to 1/0. The relevant fractions were concentrated to afford methyl 2-(7-chloro-1H-benzo[d]imidazole-2-carbonyl)-1,2,3,4-tetrahydroisoquinoline-1-carboxylate. LC-MS: 370.2 $[M+H]^+$.

[00445] Step D: To a solution of methyl 2-(7-chloro-1H-benzo[d]imidazole-2-carbonyl)-1,2,3,4-tetrahydroisoquinoline-1-carboxylate (100 mg, 0.270 mmol) in THF (2.00 mL) was added MeLi (0.50 mL) under nitrogen at 0 °C. Then the resulting mixture was allowed to warm to 25 °C slowly under nitrogen and stirred for 3 h. The mixture was poured into H₂O (2.00 mL) and extracted with EtOAc (2.00 mL x 2). The combined organic layers were dried over Na₂SO₄, filtered, and concentrated under vacuum to give a residue which was purified by preparative HPLC (Phenomenex Luna C18 column (100 × 40 mm, 5 μm); flow rate: 25 mL/min; gradient: 45% – 75 % B over 8 min; mobile phase A: 0.04% aqueous HCl mobile phase B: acetonitrile). The relevant fractions were lyophilized to afford (7-chloro-1H-benzo[d]imidazol-2-yl)(1-(2-hydroxypropan-2-yl)-3,4-dihydroisoquinolin-2(1H)-yl)methanone. LC-MS: 370.1 [M+H]⁺. ¹H NMR (400 MHz, DMSO-*d*₆) δ 7.59 – 7.48 (m, 1H), 7.45 – 7.26 (m, 3H), 7.24 – 7.11 (m, 3H), 6.86 – 5.50 (m, 1H), 5.05 – 4.47 (m, 1H), 4.37 – 3.82 (m, 2H), 3.05 – 2.87 (m, 2H), 1.35 – 1.26 (s, 3H), 1.22 (s, 3H).

Example 115: (R)-(7-Chloro-6-methyl-1H-imidazo[4,5-*b*]pyridin-2-yl)(5-methyl-7,8-dihydro-1,6-naphthyridin-6(5H)-yl)methanone



[00446] Step A: To a solution of 5-bromo-4-chloro-3-nitropyridin-2-amine (3.00 g, 12.0 mmol) in *i*-PrOH (30.0 mL) and H₂O (10.0 mL) was added Fe (3.00 g, 59.0 mmol) and NH₄Cl (2.00 g, 36.0 mmol). The mixture was stirred at 70 °C for 2 h. After cooling to room temperature, the reaction mixture was filtered and extracted with EtOAc (100 mL x 3). The combined organic layers were dried over Na₂SO₄, filtered and concentrated to give 5-bromo-4-chloropyridine-2,3-diamine. LC-MS: 221.9 [M+H]⁺.

[00447] Step B: To a solution of 5-bromo-4-chloropyridine-2,3-diamine (2.00 g, 11.0 mmol) in 2-hydroxyacetic acid (2.00 g, 22.0 mmol) was stirred at 140 °C for 2 h. The reaction mixture was quenched by saturated NaHCO₃ aqueous (100mL), filtered and concentrated under reduced pressure to give (6-bromo-7-chloro-1H-imidazo [4,5-*b*]pyridin-2-yl)methanol. LC-MS: 261.9/263.9 [M+H]⁺.

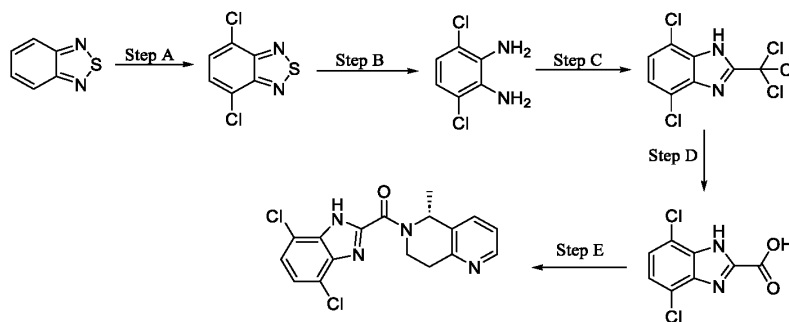
[00448] Step C: A mixture of (6-bromo-7-chloro-1H-imidazo[4,5-*b*]pyridin-2-yl)methanol (574 mg, 5.00 mmol), Pd(dppf)Cl₂.CH₂Cl₂ (249 mg, 0.305 mmol), LiOH (219 mg, 9.00 mmol) and

2,4,6-trimethyl-1,3,5,2,4,6-trioxatriborinane (800 mg, 3.00 mmol) in dioxane (20.0 mL) and H₂O (10.0 mL) was stirred at 120 °C for 12 h under nitrogen atmosphere. The reaction mixture was concentrated under reduced pressure to give a residue which was purified by preparative HPLC (column: Phenomenex luna C18 250 x 50 mm x 10 μm; mobile phase: [H₂O(0.1% TFA)-ACN]; gradient: 1%- 20% B over 10.0 min) to afford (7-chloro-6-methyl-1H-imidazo[4,5-b]pyridin-2-yl)methanol. LC-MS: 198.0 [M+H]⁺.

[00449] Step D: To a solution of (7-chloro-6-methyl-1H-imidazo[4,5-b]pyridin-2-yl)methanol (20.0 mg, 0.101 mmol) in H₂O (1.00 mL) was added Na₂CO₃ (16.0 mg, 0.152 mmol) and KMnO₄ (12.0 mg, 0.075 mmol). The mixture was stirred at 25 °C for 2 h. The reaction mixture was filtered. The filtrate was concentrated under reduced pressure to give a residue. The residue was diluted with 1N HCl (5.00 mL) and extracted with EtOAc (10.0 mL x 3). The combined organic layers were dried over Na₂SO₄, filtered and concentrated in vacuum to give 7-chloro-6-methyl-1H-imidazo[4,5-b]pyridine-2-carboxylic acid. LC-MS: 211.3 [M+H]⁺.

[100450] Step E: To a solution of 7-chloro-6-methyl-1H-imidazo[4,5-b]pyridine-2-carboxylic acid (3.00 mg, 0.014 mmol) in DCM (0.50 mL) was added TEA (4.00 mg, 0.043 mmol) and BOP-Cl (5.00 mg, 0.021 mmol). After stirred for 1 h, (R)-5-methyl-5,6,7,8-tetrahydro-1,6-naphthyridine (2.00 mg, 0.014 mmol) was added. The mixture was stirred at 25 °C for 1 h. The reaction mixture was concentrated under reduced pressure to give a residue which was purified by preparative HPLC (column: Phenomenex Luna C18 100 x 30 mm x 3 μm; mobile phase: [water (0.04% HCl) - ACN]; gradient: 10%- 40% B over 8.0 min) to afford (R)-(7-chloro-6-methyl-1H-imidazo[4,5-b]pyridin-2-yl)(5-methyl-7,8-dihydro-1,6-naphthyridin-6(5H)-yl)methanone. LC-MS: 342.1 [M+H]⁺. ¹H NMR (400 MHz, DMSO-*d*₆) δ 8.77 – 8.68 (m, 1H), 8.54 (br d, *J* = 7.9 Hz, 1H), 8.45 - 8.37 (m, 1H), 7.91 – 7.78 (m, 1H), 6.38 (q, *J* = 6.6 Hz, 0.3H), 5.95 – 5.86 (m, 0.7H), 5.41 (br dd, *J* = 5.4, 14.0 Hz, 0.6H), 4.77 (br dd, *J* = 5.8, 13.3 Hz, 0.5H), 3.29 (br d, *J* = 16.5 Hz, 3H), 2.47 (s, 3H), 1.77 (d, *J* = 6.8 Hz, 1H), 1.61 (d, *J* = 6.9 Hz, 2H).

Example 116: (R)-(4,7-Dichloro-1H-benzo[d]imidazol-2-yl)(5-methyl-7,8-dihydro-1,6-naphthyridin-6(5H)-yl)methanone

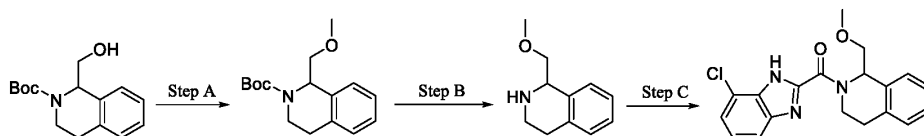


[00451] Step A: A solution of benzo[c][1,2,5]thiadiazole (1.00 g, 7.34 mmol) and 1,3-dichloro-5,5-dimethylimidazolidine-2,4-dione (2.89 g, 14.7 mmol) in H₂SO₄ (14.7 mL) was degassed and purged with O₂ three times and stirred at 20 °C for 10 min under oxygen. The mixture was stirred at 45 °C for 12 h. The mixture was poured into H₂O (40.0 mL). The resulting precipitate was dried under vacuum to give 4,7-dichlorobenzo[c][1,2,5]thiadiazole. LC-MS: 204.2 [M+H]⁺.

[00452] Step B: To a solution of 4,7-dichlorobenzo[c][1,2,5]thiadiazole (1.00 g, 4.88 mmol) in EtOH (20.0 mL) was added NaBH₄ (369 mg, 9.75 mmol). The mixture stirred at 20 °C for 19 h. The reaction mixture was poured into H₂O (20.0 mL) and washed with EtOAc (20.0 mL x 3). The combined organic layers were dried over Na₂SO₄, filtered, and concentrated under vacuum to give a residue which was purified by flash silica gel chromatography using a gradient of EtOAc/petroleum ether from 0/1 to 1/5 to afford 3,6-dichlorobenzene-1,2-diamine. LC-MS: 177.1 [M+H]⁺.

[00453] Steps C, D, and E: (R)-(4,7-Dichloro-1H-benzo[d]imidazol-2-yl)(5-methyl-7,8-dihydro-1,6-naphthyridin-6(5H)-yl)methanone was prepared from 3,6-dichlorobenzene-1,2-diamine according to the procedure of Example 30, Steps A, B, and C. LC-MS: 361.0 [M+H]⁺. ¹H NMR (400 MHz, DMSO-*d*₆) δ 8.82 – 8.21 (m, 2H), 7.93 – 7.68 (m, 1H), 7.48 – 7.34 (m, 2H), 6.08 – 5.79 (m, 1H), 5.16 – 4.66 (m, 1H), 3.76 – 3.68 (m, 1H), 3.46 – 3.24 (m, 2H), 1.82 – 1.54 (m, 3H).

Example 117: (7-Chloro-1H-benzo[d]imidazol-2-yl)(1-(methoxymethyl)-3,4-dihydroisoquinolin-2(1H)-yl)methanone



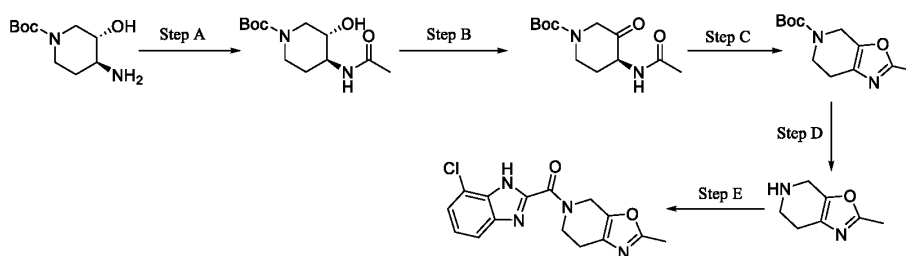
[00454] Step A: To a solution of tert-butyl 1-(hydroxymethyl)-3,4-dihydroisoquinoline-2(1H)-carboxylate (300 mg, 1.14 mmol) and MeI (6.84 g, 48.2 mmol) in THF (6.00 mL) was added *n*-BuLi (2.5 M, 1.37 mL) at –78 °C. The mixture was stirred at –78 °C for 4 h under nitrogen. Then the mixture was stirred at 20 °C for 12 h. The mixture was poured into H₂O (20.0 mL) and extracted with EtOAc (20.0 mL x 3). The combined organic layers were dried over Na₂SO₄, filtered, and concentrated under vacuum to give a residue which was purified by flash silica gel chromatography using a gradient of EtOAc/petroleum ether from 0/1 to 1/5 to afford tert-butyl 1-(methoxymethyl)-3,4-dihydroisoquinoline-2(1H)-carboxylate. LC-MS: 178.3 [M–Boc+H]⁺.

[00455] Step B: To a solution of tert-butyl 1-(methoxymethyl)-3,4-dihydroisoquinoline-2(1H)-carboxylate (100 mg, 0.361 mmol) in EtOAc (0.500 mL) was added HCl/EtOAc (4.0 M, 5.00 mL). The resulting mixture was stirred at 20 °C for 2 h. The mixture was concentrated under

vacuum at 30 °C to give 1-(methoxymethyl)-1,2,3,4-tetrahydroisoquinoline. LC-MS: 178.2 [M+H]⁺.

[00456] Step C: To a solution of 7-chloro-1H-benzo[d]imidazole-2-carboxylic acid (41.4 mg, 0.211 mmol) in DCM (1.00 mL) was added BOP-Cl (80.4 mg, 0.316 mmol) and TEA (63.9 mg, 0.632 mmol) at 0 °C. The mixture was stirred at 20 °C for 1 h. Then 1-(methoxymethyl)-1,2,3,4-tetrahydroisoquinoline (45.0 mg, 0.211 mmol) was added to the above solution and stirred at 20 °C for 2 h. The mixture was poured into water (2.00 mL) and extracted with DCM (3.00 mL x 3). The combined organic layers were dried over Na₂SO₄, filtered, and concentrated under vacuum to give a residue which was purified by preparative HPLC (Phenomenex Gemini C18 column (100 × 40 mm, 5 μm); flow rate: 25 mL/min; gradient: 40% – 70% B over 8 min; mobile phase A: 0.04% aqueous HCl, mobile phase B: acetonitrile) to afford (7-chloro-1H-benzo[d]imidazol-2-yl)(1-(methoxymethyl)-3,4-dihydroisoquinolin-2(1H)-yl)methanone. LC-MS: 356.1 [M+H]⁺. ¹H NMR (400 MHz, CDCl₃) δ 7.62 (br d, *J* = 8.5 Hz, 1H), 7.39 – 7.32 (m, 1H), 7.28 (br d, *J* = 3.6 Hz, 1H), 7.26 – 7.13 (m, 4H), 6.95 – 6.06 (m, 1H), 6.04 – 4.78 (m, 1H), 4.01 – 3.44 (m, 3H), 3.41 – 3.37 (m, 3H), 3.27 – 3.05 (m, 1H), 3.01 – 2.88 (m, 1H).

Example 118: (7-Chloro-1H-benzo[d]imidazol-2-yl)(2-methyl-6,7-dihydrooxazolo[5,4-c]pyridin-5(4H)-yl)methanone



[00457] Step A: To a mixture of *tert*-butyl (3*S*,4*S*)-4-amino-3-hydroxypiperidine-1-carboxylate (500 mg, 2.31 mmol) and TEA (281 mg, 2.77 mmol) in DCM (10.0 mL) was added acetyl chloride (200 mg, 2.54 mmol) at 0 °C. The resulting mixture was stirred at 25 °C for 1 h. The reaction mixture was poured into H₂O (15.0 mL) and extracted with DCM (15.0 mL x 5). The combined organic layers were dried over Na₂SO₄, filtered, and concentrated under vacuum to give a residue, which was purified by flash silica gel chromatography using a gradient of EtOAc/petroleum ether from 0/1 to 1/0 to afford *tert*-butyl (3*S*,4*S*)-4-acetamido-3-hydroxypiperidine-1-carboxylate. ¹H NMR (400 MHz, CDCl₃) δ 5.69 - 5.41 (m, 1H), 4.49 - 4.14 (m, 2H), 3.83 - 3.66 (m, 1H), 3.45 - 3.28 (m, 1H), 2.83 - 2.53 (m, 2H), 2.10 - 2.06 (m, 3H), 2.00 - 1.82 (m, 1H), 1.62 - 1.39 (m, 1H).

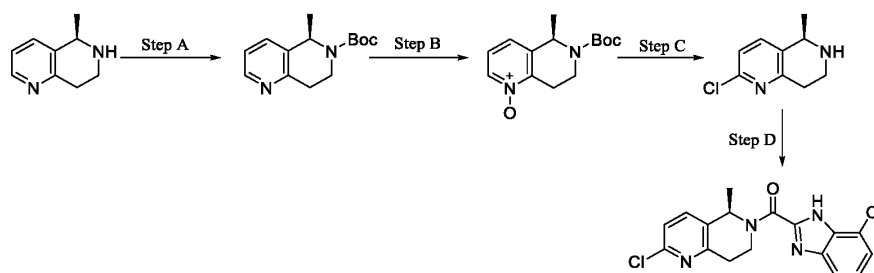
[00458] Step B: To a solution of *tert*-butyl (3*S*,4*S*)-4-acetamido-3-hydroxypiperidine-1-carboxylate (440 mg, 1.70 mmol) in DCM (15.0 mL) was added DMP (1.08 g, 2.56 mmol) at 0 °C. The resulting mixture was stirred at 25 °C for 12 h. The reaction mixture was poured into saturated NaHSO₃ aqueous (20.0 mL) and saturated NaHCO₃ aqueous (20.0 mL). The mixture was stirred until the white solid disappeared. The product was extracted with DCM (15.0 mL x 5). The combined organic layers were dried over Na₂SO₄, filtered, and concentrated under vacuum to give *tert*-butyl (*S*)-4-acetamido-3-oxopiperidine-1-carboxylate, which was used next step directly without any further purification. ¹H NMR (400 MHz, CDCl₃) 6.43 - 6.10 (m, 1H), 4.38 - 4.26 (m, 1H), 4.01 - 3.85 (m, 1H), 3.62 - 3.29 (m, 1H), 2.76 - 2.59 (m, 1H), 2.13 - 2.00 (m, 3H), 1.68 - 1.53 (m, 3H), 1.52 - 1.45 (m, 9H).

[00459] Step C: To a solution of *tert*-butyl (3*S*,4*S*)-4-acetamido-3-hydroxypiperidine-1-carboxylate (440 mg, 1.70 mmol) in DCM (15.0 mL) was added DMP (1.08 g, 2.56 mmol) at 0 °C. The resulting mixture was stirred at 25 °C for 12 h. The reaction mixture was poured into saturated NaHSO₃ aqueous (20.0 mL) and saturated NaHCO₃ aqueous (20.0 mL). The mixture was stirred until the white solid disappeared. The product was extracted with DCM (15.0 mL x 5). The combined organic layers were dried over Na₂SO₄, filtered, and concentrated under vacuum to give *tert*-butyl (*S*)-4-acetamido-3-oxopiperidine-1-carboxylate, which was used next step directly without any further purification. LC-MS: 239.3 [M+H]⁺.

[00460] Step D: To a solution of *tert*-butyl 2-methyl-6,7-dihydrooxazolo[5,4-*c*]pyridine-5(4*H*)-carboxylate (140 mg, 0.588 mmol) in EtOAc (3.00 mL) was added HCl/EtOAc (4M, 7.00 mL). The mixture was stirred at 25 °C for 30 min. The reaction mixture was concentrated under vacuum to give 2-methyl-4,5,6,7-tetrahydrooxazolo[5,4-*c*]pyridine.

[00461] Step E: To a stirred solution of 2-methyl-4,5,6,7-tetrahydrooxazolo[5,4-*c*]pyridine (120 mg, 0.687 mmol, HCl salt) and 7-chloro-1*H*-benzo[d]imidazole-2-carboxylic acid (135 mg, 0.687 mmol) in DMF (2.00 mL) was added DIEA (266 mg, 2.06 mmol), followed by HATU (131 mg, 0.344 mmol). The mixture was stirred at 20 °C for 1 h. The mixture solution was used for purification via preparative HPLC (column: Phenomenex luna C18 100*40mm*5 μm; mobile phase: [H₂O(0.04% HCl)-ACN]; gradient: 20%-50% B over 8.0 min) to afford (7-chloro-1*H*-benzo[d]imidazol-2-yl)(2-methyl-6,7-dihydrooxazolo[5,4-*c*]pyridin-5(4*H*)-yl)methanone. LC-MS: 317.1 [M+H]⁺. ¹H NMR (400 MHz, DMSO-*d*₆) δ 7.63 - 7.50 (m, 1H), 7.41 - 7.23 (m, 2H), 5.63 - 5.45 (m, 1H), 4.84 - 4.71 (m, 1H), 4.61 - 4.50 (m, 1H), 4.09 - 3.92 (m, 1H), 2.74 - 2.57 (m, 2H), 2.44 - 2.35 (m, 3H).

Example 119: (R)-(7-Chloro-1*H*-benzo[d]imidazol-2-yl)(2-chloro-5-methyl-7,8-dihydro-1,6-naphthyridin-6(5*H*)-yl)methanone



[00462] Step A: To a solution of (R)-5-methyl-5,6,7,8-tetrahydro-1,6-naphthyridine (1.00 g, 5.42 mmol) in DCM (15.0 mL) was added Boc_2O (5.91 g, 27.1 mmol) and TEA (1.64 g, 16.3 mmol). The mixture was stirred at 20 °C for 12 h. The reaction mixture was concentrated under vacuum to give a residue which was purified by flash silica gel chromatography using a gradient of EtOAc/petroleum ether from 0/1 to 1/0 to afford tert-butyl (R)-5-methyl-7,8-dihydro-1,6-naphthyridine-6(5H)-carboxylate. LC-MS: 249.1 $[\text{M}+\text{H}]^+$.

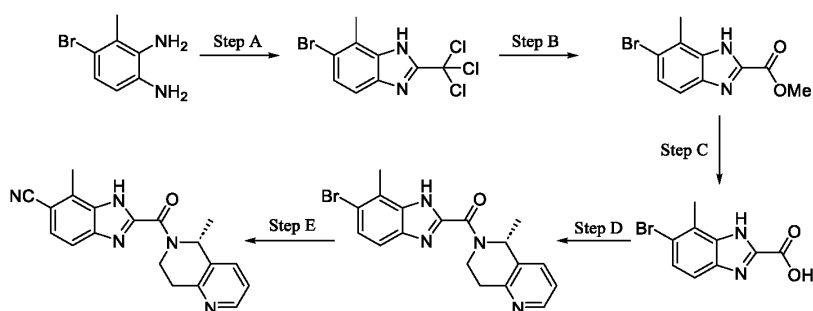
[00463] Step B: To a solution of tert-butyl (R)-5-methyl-7,8-dihydro-1,6-naphthyridine-6(5H)-carboxylate (0.50 g, 2.01 mmol) in DCM (10.0 mL) was added m-CPBA (869 mg, 4.03 mmol) at 0 °C. The mixture was stirred at 25 °C for 2 h. The residue was diluted with Na_2CO_3 (10.0 mL) and extracted with DCM (10.0 mL $\times$ 3). The combined organic layers were dried over Na_2SO_4 , filtered and concentrated under reduced pressure to give a residue which was purified by flash silica gel chromatography using a gradient of EtOAc/petroleum ether from 0/1 to 1/0 to afford (R)-6-(tert-butoxycarbonyl)-5-methyl-5,6,7,8-tetrahydro-1,6-naphthyridine 1-oxide. LC-MS: 265.2 $[\text{M}+\text{H}]^+$.

[00464] Step C: A solution of (R)-6-(tert-butoxycarbonyl)-5-methyl-5,6,7,8-tetrahydro-1,6-naphthyridine 1-oxide (50.0 mg, 0.189 mmol) in POCl_3 (0.50 mL) was stirred at 80 °C for 2 h. The reaction mixture was poured into H_2O (2.00 mL) and extracted with EtOAc (2.00 mL $\times$ 4). The combined organic layers were concentrated in vacuum to give (R)-2-chloro-5-methyl-5,6,7,8-tetrahydro-1,6-naphthyridine. LC-MS: 362.2 $[\text{M}+\text{H}]^+$.

[00465] Step D: A mixture of (R)-2-chloro-5-methyl-5,6,7,8-tetrahydro-1,6-naphthyridine (45.0 mg, 0.205 mmol), 4-chloro-1H-benzimidazole-2-carboxylic acid (40.4 mg, 0.205 mmol), DIEA (79.6 mg, 0.616 mmol) and HATU (39.1 mg, 0.103 mmol) in DMF (1.00 mL) was stirred at 20 °C for 1 h. The mixture was poured into H_2O (2.00 mL) and extracted with EtOAc (2.00 mL $\times$ 2). The combined organic layers were dried over Na_2SO_4 , filtered, and concentrated under vacuum to give a residue which was purified by preparative HPLC (Phenomenex Luna C18 column (100 $\times$ 40 mm, 5 μm); flow rate: 25 mL/min; gradient: 30% – 65% B over 8 min; mobile phase A: 0.04% aqueous HCl mobile phase B: acetonitrile). The relevant fractions were lyophilized to afford (R)-(7-chloro-1H-benzo[d]imidazol-2-yl)(2-chloro-5-methyl-7,8-dihydro-

1,6-naphthyridin-6(5H-yl)methanone. LC-MS: 361.0 $[M+H]^+$. 1H NMR (400 MHz, $CDCl_3$) δ 7.74 - 7.61 (m, 1H), 7.61 - 7.47 (m, 1H), 7.43 - 7.28 (m, 2H), 7.24 (br s, 1H), 6.41 - 5.74 (m, 1H), 5.11 - 3.66 (m, 1H), 3.45 - 3.00 (m, 2H), 1.77 (br d, $J = 6.8$ Hz, 2H), 1.62 (br d, $J = 6.9$ Hz, 2H).

Example 120: (R)-7-Methyl-2-(5-methyl-5,6,7,8-tetrahydro-1,6-naphthyridine-6-carbonyl)-1H-benzo[d]imidazole-6-carbonitrile



[00466] Step A: To a solution of 4-bromo-3-methylbenzene-1,2-diamine (3.00 g, 14.9 mmol) in AcOH (30.0 mL) was added methyl 2,2,2-trichloroacetimidate (2.63 g, 2.04 mmol). The mixture was stirred at 20 °C for 1 h. The reaction mixture was poured into H₂O (50.0 mL), then the precipitate formed. And the reaction mixture was filtered and the cake was washed with H₂O (10.0 mL x 3) to give 6-bromo-7-methyl-2-(trichloromethyl)-1H-benzo[d]imidazole. LC-MS: 327.0 $[M+H]^+$.

[00467] Step B: A solution of Na_2CO_3 (1.58 g, 14.9 mmol) in H₂O (15.0 mL) was added to a solution of 6-bromo-7-methyl-2-(trichloromethyl)-1H-benzo[d]imidazole (4.90 g, 14.9 mmol) and MeOH (196 mL). The solution was heated at 100 °C for 24 h. The mixture was poured into water (20.0 mL) and extracted with EtOAc (30.0 mL x 3). The combined organic layers were dried over Na_2SO_4 , filtered, and concentrated under vacuum to give methyl 6-bromo-7-methyl-1H-benzo[d]imidazole-2-carboxylate. LC-MS: 269.0 $[M+H]^+$.

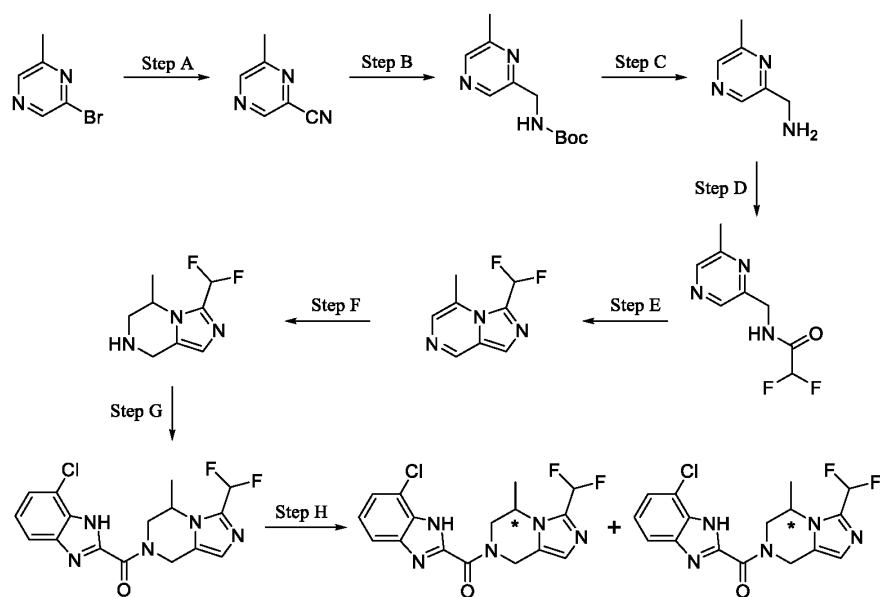
[00468] Step C: To a solution of methyl 6-bromo-7-methyl-1H-benzo[d]imidazole-2-carboxylate (100 mg, 0.372 mmol) in THF (3.00 mL) and H₂O (1.00 mL) was added LiOH (31.2 mg, 1.30 mmol). The mixture was stirred at 0 °C for 1 h. Then the mixture was stirred at 20 °C for 12 h. The aqueous phase was neutralized to pH 5 – 6 using 1M HCl and then the precipitate was filtered. The reaction mixture was filtered and the filter cake was washed with H₂O (2.00 mL), dried in vacuum to give 6-bromo-7-methyl-1H-benzo[d]imidazole-2-carboxylic acid. LC-MS: 255.1 $[M+H]^+$.

[00469] Step D: To a solution of 6-bromo-7-methyl-1H-benzo[d]imidazole-2-carboxylic acid (40.0 mg, 0.157 mmol) in DCM (1.00 mL) was added TEA (47.6 mg, 0.470 mmol) and BOP-Cl

(60.0 mg, 0.235 mmol) at 0 °C. The mixture was stirred at 25 °C for 1 h. Then (R)-5-methyl-5,6,7,8-tetrahydro-1,6-naphthyridine (23.2 mg, 0.126 mmol) was added to the above solution and stirred at 25 °C for 2 h. The mixture was poured into water (2.00 mL) and extracted with DCM (3.00 mL x 3). The combined organic layers were dried over Na₂SO₄, filtered and concentrated under vacuum to give a residue. The organic layer was which was purified by flash silica gel chromatography using a gradient of petroleum/EtOAc ether from 1/0 to 1/1 to give (R)-(6-bromo-7-methyl-1H-benzo[d]imidazol-2-yl)(5-methyl-7,8-dihydro-1,6-naphthyridin-6(5H)-yl)methanone. LC-MS: 385.2 [M+H]⁺.

[00470] Step E: To a solution of (R)-(6-bromo-7-methyl-1H-benzo[d]imidazol-2-yl)(5-methyl-7,8-dihydro-1,6-naphthyridin-6(5H)-yl)methanone (50.0 mg, 0.130 mmol), Zn(CN)₂ (18.3 mg, 0.156 mmol) in DMF (2.00 mL) was added Brettphos Pd G3 (11.8 mg, 0.013 mmol) under nitrogen. The mixture was stirred at 100 °C for 5 h. The mixture was poured into water (2.00 mL) and extracted with EtOAc (3.00 mL x 3). The combined organic layers were dried over Na₂SO₄, filtered, and concentrated under vacuum to give a residue which was purified by preparative HPLC (Phenomenex Gemini C18 column (150 × 40 mm, 10 μm); flow rate: 25 mL/min; gradient: 25% – 55% B over 6 min; mobile phase A: 10 mM NH₄HCO₃, mobile phase B: acetonitrile) to afford (R)-7-methyl-2-(5-methyl-5,6,7,8-tetrahydro-1,6-naphthyridine-6-carbonyl)-1H-benzo[d]imidazole-6-carbonitrile. LC-MS: 332.1 [M+H]⁺. ¹H NMR (400 MHz, DMSO-*d*₆) δ 14.00 – 13.41 (m, 1H), 8.60 – 8.25 (m, 1H), 7.90 – 7.73 (m, 1H), 7.70 – 7.49 (m, 2H), 7.35 – 7.16 (m, 1H), 6.55 – 5.69 (m, 1H), 5.63 – 4.67 (m, 1H), 3.82 – 3.38 (m, 1H), 3.27 – 2.90 (m, 2H), 2.85 – 2.70 (m, 3H), 1.77 – 1.51 (m, 3H).

Example 121A and 121B: (R) or (S)-(7-Chloro-1H-benzo[d]imidazol-2-yl)(3-(difluoromethyl)-5-methyl-5,6-dihydroimidazo[1,5-a]pyrazine-7(8H)-yl)methanone and (R) or (S)-(7-Chloro-1H-benzo[d]imidazol-2-yl)(3-(difluoromethyl)-5-methyl-5,6-dihydroimidazo[1,5-a]pyrazin-7(8H)-yl)methanone



[00471] Step A: A mixture of 2-bromo-6-methyl-pyrazine (10.0 g, 57.8 mmol), CuI (27.5 g, 145 mmol), 18-CROWN-6 (1.07 g, 4.04 mmol), Pd(PPh₃)₄ (1.00 g, 0.868 mmol) and KCN (9.40 g, 145 mmol) in DMF (150 mL) was stirred at 20 °C for 30 min. Then the mixture was heated to 150 °C for 3 h. The reaction mixture was allowed to cool to room temperature, poured into water (500 mL) and extracted with EtOAc (500 mL x 3). The combined organic layers were dried over Na₂SO₄, filtered, and concentrated under vacuum to give a residue which was purified by flash silica gel chromatography using a gradient of EtOAc/petroleum ether from 1/100 to 1/20 to afford 6-methylpyrazine-2-carbonitrile. LC-MS: 120.2 [M+H]⁺.

[00472] Step B: To a solution of Raney Ni (2.00 g, 28.5 mmol) in MeOH (100 mL) was added 6-methylpyrazine-2-carbonitrile (3.40 g, 28.5 mmol) and Boc₂O (6.86 g, 31.4 mmol). The mixture was degassed and purged with hydrogen three times and stirred at 20 °C for 24 h under hydrogen. The suspension was filtered through a pad of Celite and the pad was washed with EtOAc (10.0 mL x 3). The combined filtrates were concentrated under vacuum to give a residue which was purified by flash silica gel chromatography using a gradient of EtOAc/petroleum ether from 0/1 to 1/5 to afford tert-butyl ((6-methylpyrazin-2-yl)methyl)carbamate. LC-MS: 224.2 [M+H]⁺.

[00473] Step C: To a solution of tert-butyl ((6-methylpyrazin-2-yl)methyl)carbamate (2.70 g, 12.1 mmol) in EtOAc (10.0 mL) was added HCl/EtOAc (4M, 50.0 mL). The resulting mixture was stirred at 20 °C for 1 h. The mixture was concentrated under vacuum at 30 °C to give (6-methylpyrazin-2-yl)methanamine. LC-MS: 124.2 [M+H]⁺.

[00474] Step D: To a solution of (6-methylpyrazin-2-yl)methanamine (400 mg, 2.51 mmol) in DCM (8.00 mL) was added 2,2-difluoroacetic anhydride (523 mg, 3.01 mmol) at 0 °C. The mixture was stirred at 20 °C for 1 h. The reaction mixture was concentrated under vacuum to give the crude product which was purified by flash silica gel chromatography using a gradient of EtOAc/petroleum ether from 0/1 to 2/5 to afford 2,2-difluoro-N-((6-methylpyrazin-2-yl)methyl)acetamide. LC-MS: 202.2 [M+H]⁺.

[00475] Step E: To a solution of 2,2-difluoro-N-((6-methylpyrazin-2-yl)methyl)acetamide (250 mg, 1.24 mmol) in POCl₃ (2.00 mL) was added P₂O₅ (221 mg, 1.55 mmol). The mixture was stirred at 100 °C for 12 h. The mixture was concentrated, and the residue was poured into ice-water (3.00 mL), basified with NaHCO₃ (solid) to pH 8, then extracted with DCM (5.00 mL x 2). The combined organic phase was washed with water (5.00 mL x 2) and brine (5.00 mL), dried over Na₂SO₄, filtered, and concentrated to give 3-(difluoromethyl)-5-methylimidazo[1,5-a]pyrazine. LC-MS: 184.2 [M+H]⁺.

[00476] Step F: To a solution of 10% palladium on carbon (150 mg) in trifluoroethanol (3.00 mL) was added 3-(difluoromethyl)-5-methylimidazo[1,5-a]pyrazine (150 mg, 0.819 mmol). The mixture was stirred at 25 °C for 3 h under hydrogen (15 Psi). The suspension was filtered through a pad of Celite. The combined filtrates were concentrated under vacuum to give 3-(difluoromethyl)-5-methyl-5,6,7,8-tetrahydroimidazo[1,5-a]pyrazine. LC-MS: 188.2 [M+H]⁺.

[00477] Step G: To a solution of 3-(difluoromethyl)-5-methyl-5,6,7,8-tetrahydroimidazo[1,5-a]pyrazine (50.0 mg, 0.267 mmol) and 7-chloro-1H-benzo[d]imidazole-2-carboxylic acid (52.5 mg, 0.267 mmol) in DMF (1.00 mL) was added DIEA (104 mg, 0.801 mmol) and HATU (102 mg, 0.267 mmol). The mixture was stirred at 25 °C for 1 h. The mixture was poured into water (2.00 mL) and extracted with EtOAc (3.00 mL x 3). The combined organic layers were dried over Na₂SO₄, filtered, and concentrated under vacuum to give a residue which was purified by preparative TLC (pure EtOAc, R_f = 0.54) to afford (7-chloro-1H-benzo[d]imidazol-2-yl)(3-(difluoromethyl)-5-methyl-5,6-dihydroimidazo[1,5-a]pyrazin-7(8H)-yl)methanone. LC-MS: 366.2 [M+H]⁺.

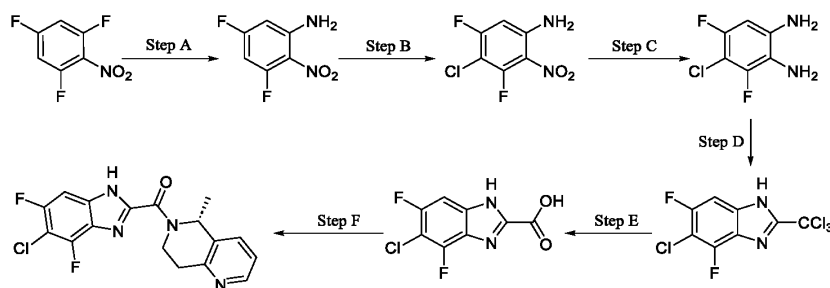
[00478] Step H: (7-Chloro-1H-benzo[d]imidazol-2-yl)(3-(difluoromethyl)-5-methyl-5,6-dihydroimidazo[1,5-a]pyrazin-7(8H)-yl)methanone (70.0 mg, 0.191 mmol) was further separated by SFC separation((Phenomenex-Cellulose-2(250 × 30 mm, 10 μm); flow rate: 70 mL/min; gradient: 45 – 45% B over 7.5 min; mobile phase A: CO₂, mobile phase B: MeOH(0.1%NH₃H₂O)) to afford ((R)-(7-chloro-1H-benzo[d]imidazol-2-yl)(3-(difluoromethyl)-5-methyl-5,6-dihydroimidazo[1,5-a]pyrazin-7(8H)-yl)methanone (first eluent) and (S)-(7-chloro-

1H-benzo[d]imidazol-2-yl)(3-(difluoromethyl)-5-methyl-5,6-dihydroimidazo[1,5-a]pyrazin-7(8H)-yl)methanone (second eluent).

[00479] First eluted compound (**Example 121A**): LC-MS: 366.0 [M+H]⁺. ¹H NMR (400 MHz, CD₃OD) δ 7.68 – 7.47 (m, 1H), 7.45 – 7.23 (m, 2H), 7.06 – 6.75 (m, 2H), 5.55 – 5.02 (m, 1H), 4.99 – 4.87 (m, 2H), 4.74 – 4.48 (m, 1H), 3.98 – 3.53 (m, 1H), 1.55 (br d, *J* = 6.4 Hz, 3H).

Second eluted compound (**Example 121B**): LC-MS: 366.1 [M+H]⁺. ¹H NMR (400 MHz, CD₃OD) δ 7.66 – 7.51 (m, 1H), 7.41 – 7.27 (m, 2H), 7.06 – 6.74 (m, 2H), 5.60 – 5.03 (m, 1H), 4.99 – 4.87 (m, 2H), 4.73 – 4.56 (m, 1H), 4.00 – 3.49 (m, 1H), 1.55 (br d, *J* = 4.5 Hz, 3H). The absolute stereochemistry for the first and second eluted compounds was not determined.

Example 122: (R)-(5-Chloro-4,6-difluoro-1H-benzo[d]imidazol-2-yl)(5-methyl-7,8-dihydro-1,6-naphthyridin-6(5H)-yl)methanone



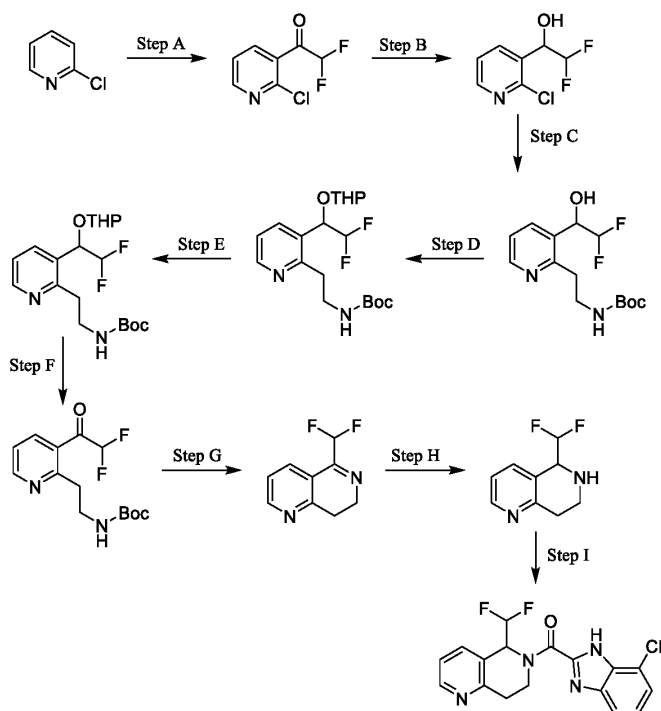
[00480] Step A: To a solution of 1,3,5-trifluoro-2-nitrobenzene (1.00 g, 5.65 mmol) in THF (8.00 mL) was added NH₃/MeOH (7M, 3.20 mL) at 0 °C under nitrogen atmosphere. The mixture was stirred at 25 °C for 12 h. The reaction mixture was poured into H₂O (10.0 mL) and extracted with EtOAc (10.0 mL x 3). The combined organic layers were dried over Na₂SO₄, filtered, and concentrated under vacuum to give a residue which was purified by flash silica gel chromatography using a gradient of petroleum/EtOAc ether from 6/1 to 5/1 to afford 3,5-difluoro-2-nitroaniline. ¹H NMR (400 MHz, DMSO-*d*₆) δ 7.34 (br s, 2H), 6.62 – 6.51 (m, 2H).

[00481] Step B: To a solution of 3,5-difluoro-2-nitroaniline (500 mg, 2.87 mmol) in MeCN (15.0 mL) was added NCS (383 mg, 2.87 mmol). The mixture was stirred at 70 °C for 12 h. The reaction mixture was poured into H₂O (20.0 mL) and extracted with EtOAc (20.0 mL x 3). The combined organic layers were dried over Na₂SO₄, filtered, and concentrated under vacuum to give a residue which was purified by flash silica gel chromatography using a gradient of petroleum/EtOAc ether from 8/1 to 7/1 to afford 4-chloro-3,5-difluoro-2-nitroaniline. LC-MS: 207.0 [M+H]⁺.

[00482] Steps C, D, E, and F: (R)-(5-Chloro-4,6-difluoro-1H-benzo[d]imidazol-2-yl)(5-methyl-7,8-dihydro-1,6-naphthyridin-6(5H)-yl)methanone was prepared from 4-chloro-3,5-

difluoro-2-nitroaniline according to the procedure of Example 84, Steps A, B, C, and D. LC-MS: 363.1 [M+H]⁺. ¹H NMR (400 MHz, DMSO-*d*₆) δ 14.08 – 13.66 (m, 1H), 8.77 – 8.54 (m, 1H), 8.39 – 8.05 (m, 1H), 7.81 – 7.36 (m, 2H), 6.57 – 4.70 (m, 2H), 3.75 – 3.69 (m, 1H), 3.44 – 3.31 (m, 1H), 3.16 (br d, *J* = 16.8 Hz, 1H), 1.83 – 1.49 (m, 3H).

Example 123: (7-Chloro-1H-benzo[d]imidazol-2-yl)(5-(difluoromethyl)-7,8-dihydro-1,6-naphthyridin-6(5H)-yl)methanone



[00483] Step A: To a stirred solution of diisopropylamine (70.0 g, 444 mmol) in THF (480 mL) at -78 °C was added *n*-BuLi (2.5M, 170 mL) dropwise under nitrogen. The reaction mixture was stirred at -78 °C for 30 min. And then 2-chloropyridine (24.0 g, 211 mmol) was added dropwise. The resulting yellow solution was stirred at -78 °C for 3 h. Ethyl 2,2-difluoroacetate (32.0 g, 254 mmol) was then added dropwise. The mixture was stirred at -78 °C for 1 h. The reaction mixture was poured into saturated aqueous NH₄Cl (200 mL) and extracted with EtOAc (200 mL x 3). The combined organic layers were dried over MgSO₄, filtered, and concentrated under vacuum to give 1-(2-chloropyridin-3-yl)-2,2-difluoroethan-1-one.

[00484] Step B: A mixture 1-(2-chloro-3-pyridyl)-2,2-difluoro-ethanone (36.0 g, 186 mmol) and NaBH₄ (14.2 g, 375 mmol) in MeOH (1.44 L) was stirred at 0 °C for 1 h. The reaction mixture was poured into H₂O (800 mL) and extracted with DCM (800 mL x 5). The combined organic layers were dried over Na₂SO₄, filtered, and concentrated under vacuum to give a residue which was purified by flash silica gel chromatography using a gradient of EtOAc/petroleum

ether from 0/1 to 1/1 to afford 1-(2-chloropyridin-3-yl)-2,2-difluoroethan-1-ol. LC-MS: 194.1 [M+H]⁺.

[00485] Step C: A mixture of 1-(2-chloro-3-pyridyl)-2,2-difluoro-ethanol (5.60 g, 29 mmol), DHP (3.60 g, 43.4 mmol, 4.0 mL) and PPTS (726 mg, 2.90 mmol) in DCM (260 mL) was stirred at 50 °C for 4 h. The reaction mixture was poured into H₂O (50.0 mL) and extracted with DCM (50.0 mL x 3). The combined organic layers were dried over Na₂SO₄, filtered, and concentrated under vacuum to give a residue which was purified by flash silica gel chromatography using a gradient of EtOAc/petroleum ether from 1/0 to 1/1 to afford 2-chloro-3-(2,2-difluoro-1-((tetrahydro-2H-pyran-2-yl)oxy)ethyl)pyridine. LC-MS: 278.1 [M+H]⁺.

[00486] Step D: To a mixture of 2-chloro-3-(2,2-difluoro-1-tetrahydropyran-2-yloxy-ethyl)pyridine (2.5.0 g, 9.00 mmol), potassium;2-(tert-butoxycarbonylamino)ethyl-trifluoroborane (2.71 g, 10.8 mmol), cataCium A Pd-G3 (656 mg, 0.900 mmol) in CPME (60.0 mL) was added Cs₂CO₃ (5.87 g, 18.0 mmol). The mixture was degassed and purged with nitrogen for 3 times, and then the mixture was stirred at 80 °C for 12 h under nitrogen atmosphere. The reaction mixture was poured into H₂O (20.0 mL) and extracted with EtOAc (20.0 mL x 3). The combined organic layers were dried over Na₂SO₄, filtered, and concentrated under vacuum to give a residue which was purified by flash silica gel chromatography using a gradient of EtOAc/petroleum ether from 0/1 to 1/1 to afford tert-butyl (2-(3-(2,2-difluoro-1-((tetrahydro-2H-pyran-2-yl)oxy)ethyl)pyridin-2-yl)ethyl)carbamate. LC-MS: 387.3 [M+H]⁺.

[00487] Step E: A mixture of tert-butyl (2-(3-(2,2-difluoro-1-((tetrahydro-2H-pyran-2-yl)oxy)ethyl)pyridin-2-yl)ethyl)carbamate (1.65 g, 4.27 mmol) and TsOH (700 mg, 4.07 mmol) in MeOH (50.0 mL) was stirred at 60 °C for 12 h. The reaction mixture was poured into H₂O (10.0 mL) and extracted with DCM (10.0 mL x 3). The combined organic layers were dried over Na₂SO₄, filtered, and concentrated under vacuum to give a residue which was purified by flash silica gel chromatography using a gradient of EtOAc/petroleum ether from 0/1 to 1/1 to afford tert-butyl (2-(3-(2,2-difluoro-1-((tetrahydro-2H-pyran-2-yl)oxy)ethyl)pyridin-2-yl)ethyl)carbamate. LC-MS: 303.1 [M+H]⁺.

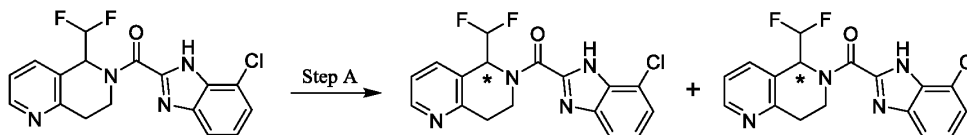
[00488] Step F: A mixture of tert-Butyl (2-(3-(2,2-difluoro-1-hydroxyethyl)pyridin-2-yl)ethyl)carbamate (320 mg, 1.06 mmol) and DMP (673 mg, 1.59 mmol) in DCM (5.00 mL) was stirred at 20 °C for 1 h. The reaction mixture was poured into H₂O (5.00 mL) and extracted with DCM (5.00 mL x 3). The combined organic layers were dried over Na₂SO₄, filtered, and concentrated under vacuum to give a residue which was purified by flash silica gel chromatography using a gradient of EtOAc/petroleum ether from 0/1 to 1/1 to afford tert-butyl (2-(3-(2,2-difluoroacetyl)pyridin-2-yl)ethyl)carbamate. LC-MS: 301.1 [M+H]⁺.

[00489] Step G: To a solution of tert-butyl (2-(3-(2,2-difluoroacetyl)pyridin-2-yl)ethyl)carbamate (90.0 mg, 0.300 mmol) in EtOAc (1.00 mL) was added HCl/EtOAc (4.0 M, 9.00 mL). The resulting mixture was stirred at 20 °C for 12 h. The mixture was concentrated under vacuum at 30 °C to give 5-(difluoromethyl)-7,8-dihydro-1,6-naphthyridine. LC-MS: 183.2 [M+H]⁺.

[00490] Step H: To a solution of 5-(difluoromethyl)-7,8-dihydro-1,6-naphthyridine (100 mg, 0.549 mmol) in MeOH (4.00 mL) was added NaBH₃CN (100 mg, 1.59 mmol). The mixture was stirred at 20 °C for 1 h. The reaction mixture was poured into H₂O (5.00 mL) and extracted with DCM (5.00 mL x 3). The combined organic layers were dried over Na₂SO₄, filtered, and concentrated under vacuum to 5-(difluoromethyl)-5,6,7,8-tetrahydro-1,6-naphthyridine. LC-MS: 185.2 [M+H]⁺.

[00491] Step I: A mixture of 5-(difluoromethyl)-5,6,7,8-tetrahydro-1,6-naphthyridine (35.0 mg, 0.190 mol), 7-chloro-1H-benzimidazole-2-carboxylic acid (41.0 mg, 0.209 mmol), HATU (36.0 mg, 0.095 mmol) and DIEA (74.0 mg, 0.570 mmol) in DMF (1.00 mL) was stirred at 20 °C for 1 h. The reaction mixture was poured into H₂O (5.00 mL) and extracted with EtOAc (5.00 mL x 3). The combined organic layers were dried over Na₂SO₄, filtered, and concentrated under vacuum to give a residue which was purified by preparative HPLC (Phenomenex Luna C18 column 100×40mm×5um); flow rate: 25 mL/min; gradient: 10% – 40% B over 8 min; mobile phase A: 0.04% aqueous HCl, mobile phase B: acetonitrile) to afford (7-chloro-1H-benzo[d]imidazol-2-yl)(5-(difluoromethyl)-7,8-dihydro-1,6-naphthyridin-6(5H)-yl)methanone. LC-MS: 363.0 [M+H]⁺. ¹H NMR (400 MHz, CDCl₃) δ 8.79 – 8.61 (m, 1H), 8.53 (br d, *J* = 7.3 Hz, 1H), 7.86 – 7.67 (m, 2H), 7.46 – 7.30 (m, 2H), 7.06 – 5.99 (m, 2H), 5.20 – 3.32 (m, 4H).

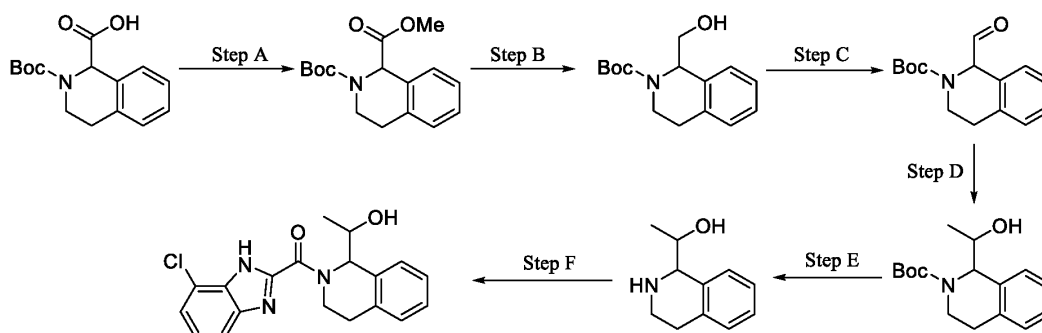
Examples 123A and 123B: (R) or (S)-(7-Chloro-1H-benzo[d]imidazol-2-yl)(5-(difluoromethyl)-7,8-dihydro-1,6-naphthyridin-6(5H)-yl)methanone and (R) or (S)-(7-Chloro-1H-benzo[d]imidazol-2-yl)(5-(difluoromethyl)-7,8-dihydro-1,6-naphthyridin-6(5H)-yl)methanone



[00492] Step A: (7-Chloro-1H-benzo[d]imidazol-2-yl)(5-(difluoromethyl)-7,8-dihydro-1,6-naphthyridin-6(5H)-yl)methanone (product of Example 123) (57.0 mg, 0.157 mmol) was further separated by chiral SFC separation ((s,s) DAICEL CHIRALPAK AD (250 × 30 mm, 10 um); flow rate: 70 mL/min; gradient: 35% B over 14 min; mobile phase A: heptane, mobile phase B: EtOH(0.1%NH₃H₂O). First eluted compound: LC-MS: 363.0 [M+H]⁺. ¹H NMR (400 MHz,

DMSO- d_6) δ 13.91 – 13.44 (m, 1H), 8.56 (br d, J = 4.8 Hz, 1H), 8.04 – 7.80 (m, 1H), 7.59 – 7.33 (m, 4H), 6.58 (br d, J = 3.1 Hz, 1H), 6.20 – 5.67 (m, 1H), 4.92 – 3.72 (m, 2H), 3.19 – 2.98 (m, 2H). Second eluted compound: LC-MS: 363.0 $[M+H]^+$. 1H NMR (400 MHz, DMSO- d_6) δ 13.66 (br d, J = 3.4 Hz, 1H), 8.62 – 8.50 (m, 1H), 8.01 – 7.77 (m, 1H), 7.62 – 7.31 (m, 4H), 6.91 – 6.39 (m, 1H), 6.26 – 5.46 (m, 1H), 4.92 – 3.57 (m, 2H), 3.21 – 3.00 (m, 2H). The absolute stereochemistry for the first and second eluted compounds was not determined.

Example 124: (7-Chloro-1H-benzo[d]imidazol-2-yl)(1-(1-hydroxyethyl)-3,4-dihydroisoquinolin-2(1H)-yl)methanone



[00493] Step A: To a solution of 2-(tert-butoxycarbonyl)-1,2,3,4-tetrahydroisoquinoline-1-carboxylic acid (2.00 g, 7.21 mmol) in DMF (25.0 mL) was added MeI (1.23 g, 8.65 mmol) and K_2CO_3 (1.20 g, 8.65 mmol) at 25 °C. The mixture was stirred at 25 °C for 2 h. The mixture was poured into H_2O (20.0 mL) and extracted with EtOAc (25.0 mL x 3). The organic layer was separated, washed with saturated aqueous NaCl, dried over anhydrous $MgSO_4$ and concentrated under vacuum to give the residue which was purified by flash silica gel chromatography using a gradient of EtOAc/petroleum ether from 0/1 to 1/1 to afford 2-(tert-butyl) 1-methyl 3,4-dihydroisoquinoline-1,2(1H)-dicarboxylate. LC-MS: 192.2 $[M-Boc+H]^+$.

[00494] Step B: To a solution of 2-(tert-butyl) 1-methyl 3,4-dihydroisoquinoline-1,2(1H)-dicarboxylate (450 mg, 1.54 mmol) in THF (10.0 mL) was added $LiBH_4$ (1M, 1.50 mL) at 0 °C. The mixture was stirred at 25 °C for 1 h. The reaction mixture was quenched by addition saturated aqueous NH_4Cl (10.0 mL), and extracted with EtOAc (10.0 mL x 3). The combined organic layers were washed with brine (10.0 mL x 3), dried over Na_2SO_4 , filtered and concentrated under vacuum to give a residue which was purified by flash silica gel chromatography using a gradient of EtOAc/petroleum ether from 1/0 to 0/1 to afford tert-butyl 1-(hydroxymethyl)-3,4-dihydroisoquinoline-2(1H)-carboxylate. LC-MS: 164.2 $[M-Boc+H]^+$.

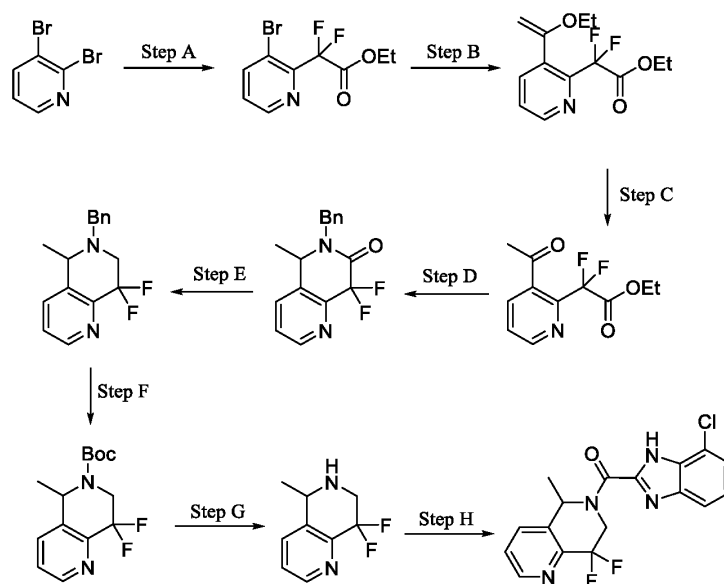
[00495] Step C: To a solution of tert-butyl 1-(hydroxymethyl)-3,4-dihydroisoquinoline-2(1H)-carboxylate (100 mg, 0.380 mmol) in DCM (6.00 mL) was added Dess-Martin (1.06 g, 2.51 mmol). The mixture was stirred at 25 °C for 12 h. The reaction mixture was poured into H_2O

(6.00 mL) and extracted with DCM (6.00 mL x 4). The combined organic layers were dried over Na₂SO₄, filtered, and concentrated under vacuum to give a residue which was purified by preparative TLC (petroleum ether: EtOAc = 5:1, R_f = 0.43) to afford tert-butyl 1-formyl-3,4-dihydroisoquinoline-2(1H)-carboxylate. LC-MS: 162.2 [M-Boc+H]⁺.

[00496] Step D: To a solution of tert-butyl 1-formyl-3,4-dihydroisoquinoline-2(1H)-carboxylate (170 mg, 0.651 mmol) in THF (3.00 mL) was added MeMgBr (2.5M, 0.40 mL). The mixture was degassed and purged with nitrogen for 3 times at 0 °C. Then the resulting mixture was allowed to warm to 25 °C slowly under nitrogen and stirred for 12 h. The reaction mixture was poured into H₂O (3.00 mL) and extracted with EtOAc (3.00 mL x 2). The combined organic layers were dried over Na₂SO₄, filtered, and concentrated under vacuum to give a residue which was purified by preparative TLC (petroleum ether: EtOAc = 5:1, R_f = 0.24) to afford tert-butyl 1-(1-hydroxyethyl)-3,4-dihydroisoquinoline-2(1H)-carboxylate. LC-MS: 178.3 [M-Boc+H]⁺.

[00497] Step E: To a solution of tert-butyl 1-(1-hydroxyethyl)-3,4-dihydroisoquinoline-2(1H)-carboxylate (70.0 mg, 0.252 mmol) in HCl/EtOAc (4M, 2.00 mL). The mixture was stirred at 25 °C for 1 h. The mixture was concentrated under vacuum to give a crude 1-(1,2,3,4-tetrahydroisoquinolin-1-yl)ethan-1-ol. LC-MS: 178.2 [M+H]⁺.

[00498] Step F: To a solution of 1-(1,2,3,4-tetrahydroisoquinolin-1-yl)ethan-1-ol (50.0 mg, 0.282 mmol) in DCM (0.50 mL) was added 7-chloro-1H-benzimidazole-2-carboxylic acid (55.5 mg, 0.282 mmol), TEA (85.6 mg, 0.846 mmol) and T₃P (50% purity, 359 mg, 0.564 mmol). The mixture was stirred at 25 °C for 1 h. The reaction mixture was poured into H₂O (2.00 mL) and extracted with DCM (1.00 mL x 3). The combined organic layers were dried over Na₂SO₄, filtered and concentrated under vacuum to give a residue which was purified by preparative HPLC (Phenomenex Luna C18 column (100 × 40 mm, 5 μm); flow rate: 25 mL/min; gradient: 35% – 65% B over 8 min; mobile phase A: 10 mM aqueous NH₄HCO₃, mobile phase B: acetonitrile) to afford (7-chloro-1H-benzo[d]imidazol-2-yl)(1-(1-hydroxyethyl)-3,4-dihydroisoquinolin-2(1H)-yl)methanone. LC-MS: 356.1 [M+H]⁺. ¹H NMR (400 MHz, DMSO-*d*₆) δ 7.57 – 7.50 (m, 1H), 7.43 – 7.28 (m, 3H), 7.25 – 7.17 (m, 3H), 6.46 – 5.46 (m, 1H), 5.42 – 4.97 (m, 1H), 4.46 – 4.29 (m, 1H), 4.20 – 3.86 (m, 2H), 3.10 – 2.92 (m, 2H), 1.26 – 1.20 (m, 2H), 1.14 – 1.08 (m, 1H).
Example 125: (7-Chloro-1H-benzo[d]imidazol-2-yl)(8,8-difluoro-5-methyl-7,8-dihydro-1,6-naphthyridin-6(5H)-yl)methanone



[00499] Step A: To a solution of Cu (5.37 g, 84.4 mmol) in DMSO (10.0 mL) was added ethyl 2-bromo-2,2-difluoroacetate (8.57 g, 42.2 mmol). The mixture was stirred at 20 °C for 1 h. Then 2,3-dibromopyridine (5.00 g, 21.1 mmol) was added and stirred at 20 °C for 12 h. The reaction mixture was quenched by saturated NH_4Cl solution (30.0 mL) and extracted with EtOAc (20.0 mL $\times$ 3). The combined organic phase was washed with brine (10.0 mL $\times$ 1), dried over anhydrous Na_2SO_4 , filtered and concentrated give a residue which was purified by flash silica gel chromatography using a gradient of EtOAc/petroleum ether from 0/100 to 1/5 to afford ethyl 2-(3-bromopyridin-2-yl)-2,2-difluoroacetate. LC-MS: 282.0/280.0 $[\text{M}+\text{H}]^+$.

[00500] Step B: To a solution of ethyl 2-(3-bromopyridin-2-yl)-2,2-difluoroacetate (4.20 g, 15.0 mmol), $\text{Pd}(\text{PPh}_3)_2\text{Cl}_2$ (2.11 g, 3.00 mmol) in DMF (60.0 mL) was added tributyl(1-ethoxyvinyl)stannane (9.75 g, 27.0 mmol) and the reaction mixture was degassed and purged with nitrogen for 3 times, then the mixture was stirred at 100 °C for 12 h under nitrogen atmosphere. The reaction mixture was allowed to cool to room temperature, poured into water (100 mL) and extracted with EtOAc (50.0 mL $\times$ 3). The combined organic layers were dried over Na_2SO_4 , filtered, and concentrated under vacuum to give a residue which was purified by flash silica gel chromatography using a gradient of EtOAc/petroleum ether from 0/100 to 1/5 to afford ethyl 2-(3-(1-ethoxyvinyl)pyridin-2-yl)-2,2-difluoroacetate. LC-MS: 272.1 $[\text{M}+\text{H}]^+$.

[00501] Step C: To a solution of ethyl 2-(3-(1-ethoxyvinyl)pyridin-2-yl)-2,2-difluoroacetate (2.00 g, 7.37 mmol) in THF (40.0 mL) and H_2O (8.00 mL) was added HCl (12M, 7.99 mL). The mixture was stirred at 20 °C for 2 h. The reaction mixture was poured into water (20.0 mL) and extracted with EtOAc (30.0 mL $\times$ 3). The combined organic layers were dried over Na_2SO_4 ,

filtered, and concentrated under vacuum to give a residue which was purified by flash silica gel chromatography using a gradient of EtOAc/petroleum ether from 0/100 to 1/5 to afford ethyl 2-(3-acetylpyridin-2-yl)-2,2-difluoroacetate. LC-MS: 244.2 [M+H]⁺.

[00502] Step D: To a solution of ethyl 2-(3-acetylpyridin-2-yl)-2,2-difluoroacetate (500 mg, 2.06 mmol) and phenylmethanamine (242 mg, 2.26 mmol) in MeOH (20.0 mL), then AcOH (123 mg, 2.06 mmol) was added to pH=5~6, the mixture was stirred at 25 °C for 30 min. Then NaBH₃CN (258 mg, 4.11 mmol) was added, the mixture was stirred at 70 °C for 12 h under autoclave. The reaction mixture was allowed to cool to room temperature, poured into water (20.0 mL) and extracted with DCM (20.0 mL x 4). The combined organic layers were dried over Na₂SO₄, filtered, and concentrated under vacuum to give a residue which was purified by flash silica gel chromatography using a gradient of EtOAc/petroleum ether from 0/1 to 1/10 to afford 6-benzyl-8,8-difluoro-5-methyl-5,8-dihydro-1,6-naphthyridin-7(6H)-one. LC-MS: 289.1 [M+H]⁺.

[00503] Step E: To a solution of 6-benzyl-8,8-difluoro-5-methyl-5,8-dihydro-1,6-naphthyridin-7(6H)-one (140 mg, 0.486 mmol) in THF (20.0 mL) was added BH₃-Me₂S (10M, 0.971 mmol) at 0 °C under nitrogen. The resulting mixture was stirred at 70 °C for 12 h. The reaction mixture was allowed to cool to 0 °C, then MeOH (5.00 mL) was added. The mixture was stirred at 70 °C for 1 h. The reaction mixture was allowed to cool to room temperature, poured into water (10.0 mL) and extracted with DCM (5.00 mL x 5). The organic layers were combined, dried over sodium sulfate, filtered and concentrated in vacuo which was purified by preparative TLC (EtOAc/petroleum ether = 1/1, R_f = 0.7) to afford 6-benzyl-8,8-difluoro-5-methyl-5,6,7,8-tetrahydro-1,6-naphthyridine. LC-MS: 275.3 [M+H]⁺.

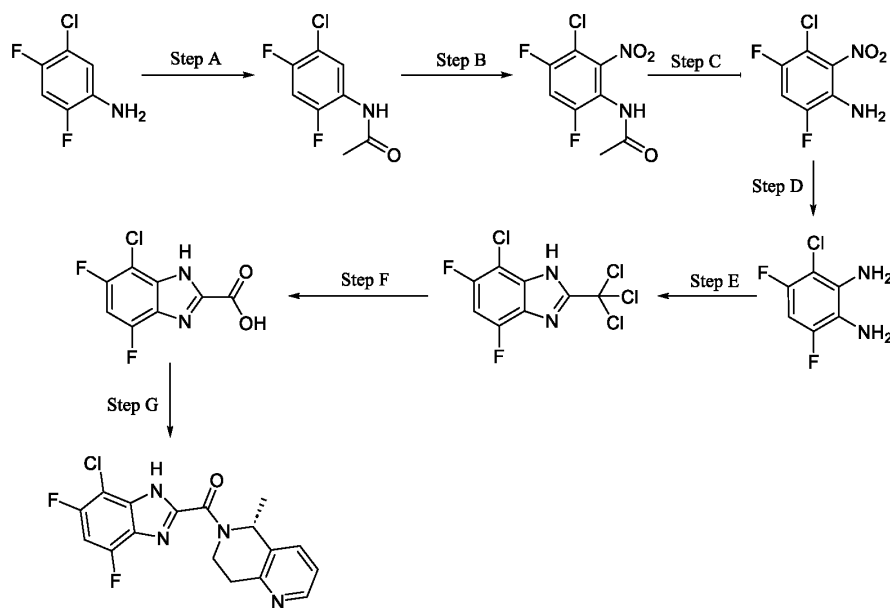
[00504] Step F: To a solution of palladium on carbon (10%, contains 67% water, 50.0 mg) in MeOH (10.0 mL) was added 6-benzyl-8,8-difluoro-5-methyl-5,6,7,8-tetrahydro-1,6-naphthyridine (50.0 mg, 0.182 mmol) and Boc₂O (39.8 mg, 0.182 mmol). The mixture was degassed and purged with hydrogen three times and stirred at 50 °C for 1 h under hydrogen (50 Psi). The reaction mixture was filtered through a pad of Celite and the filtrate was concentrated under vacuum to give a residue which was purified by preparative TLC (EtOAc/petroleum ether = 1/5, R_f = 0.3) to afford tert-butyl 8,8-difluoro-5-methyl-7,8-dihydro-1,6-naphthyridine-6(5H)-carboxylate. LC-MS: 285.2 [M+H]⁺.

[00505] Step G: To a solution of tert-butyl 8,8-difluoro-5-methyl-7,8-dihydro-1,6-naphthyridine-6(5H)-carboxylate (15.0 mg, 0.053 mmol) in EtOAc (1.00 mL) was added HCl/EtOAc (4.0 M, 2.00 mL). The resulting mixture was stirred at 20 °C for 30 min. The

mixture was concentrated under vacuum to give 8,8-difluoro-5-methyl-5,6,7,8-tetrahydro-1,6-naphthyridine. LC-MS: 185.2 $[M+H]^+$.

[00506] Step H: A mixture of 7-chloro-1H-benzo[d]imidazole-2-carboxylic acid (8.50 mg, 0.045 mmol), 8,8-difluoro-5-methyl-5,6,7,8-tetrahydro-1,6-naphthyridine (10.0 mg, 0.045 mmol), BOP-Cl (17.3 mg, 0.068 mmol) and DIEA (13.8 mg, 0.106 mmol) in DCM (1.00 mL) was stirred at 20 °C for 1 h. The reaction mixture was poured into H₂O (2.00 mL) and extracted with EtOAc (3.00 mL x 3). The combined organic layers were dried over Na₂SO₄, filtered, and concentrated under vacuum to give a residue which was purified by preparative HPLC (Phenomenex Luna C18 column (150 × 40 mm, 10 μm); flow rate: 25 mL/min; gradient: 25% – 60% B over 6 min; mobile phase A: water (10 mM NH₄HCO₃), mobile phase B: acetonitrile) to afford (7-chloro-1H-benzo[d]imidazol-2-yl)(8,8-difluoro-5-methyl-7,8-dihydro-1,6-naphthyridin-6(5H)-yl)methanone. LC-MS: 363.1 $[M+H]^+$.

Example 126: (R)-(7-Chloro-4,6-difluoro-1H-benzo[d]imidazol-2-yl)(5-methyl-7,8-dihydro-1,6-naphthyridin-6(5H)-yl)methanone



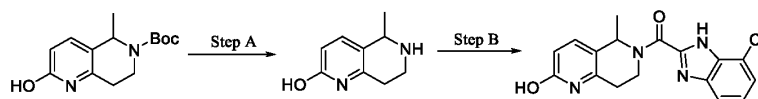
[00507] Step A: To a solution of 5-chloro-2,4-difluoroaniline (3.00 g, 18.3 mmol) in DCM (100 mL) was added TEA (5.57 g, 55.0 mmol) and Ac₂O (2.25 g, 22.0 mmol). The mixture was stirred at 25 °C for 12 h. The reaction mixture was poured into H₂O (100 mL) and extracted with EtOAc (100 mL x 3). The combined organic layers were dried over Na₂SO₄, filtered, and concentrated under vacuum to give a residue which was purified by flash silica gel chromatography using a gradient of petroleum/EtOAc ether from 1/0 to 9/1 to afford N-(5-chloro-2,4-difluorophenyl)acetamide. LC-MS: 206.1 $[M+H]^+$.

[00508] Step B: To a solution of N-(5-chloro-2,4-difluorophenyl)acetamide (1.00 g, 4.86 mmol) in H₂SO₄ (25.0 mL) was added HNO₃ (1.53 g, 24.3 mmol). The mixture was stirred at 0 °C for 1 h. The reaction mixture was poured into H₂O (50.0 mL). The precipitate was collected by filtration and dried in vacuum to give crude product which was purified by flash silica gel chromatography using a gradient of petroleum/EtOAc ether from 1/0 to 9/1 to afford N-(3-chloro-4,6-difluoro-2-nitrophenyl) acetamide. LC-MS: 251.1 [M+H]⁺.

[00509] Step C: To a solution of N-(3-chloro-4,6-difluoro-2-nitrophenyl)acetamide (450 mg, 1.80 mmol) in MeOH (20.0 mL) was added HCl aqueous (12M, 4.49 mL). The mixture was stirred at 70 °C for 12 h. The reaction mixture was poured into H₂O (20.0 mL) and extracted with EtOAc (20.0 mL x 3). The combined organic layers were washed with NaCl (aq, 10.0 mL x 3), dried over Na₂SO₄, filtered, and concentrated under vacuum to give a residue which was purified by preparative TLC (EtOAc: PE= 1:1, R_f= 0.65) to afford 3-chloro-4,6-difluoro-2-nitroaniline. LC-MS: 207.1 [M+H]⁺.

[00510] Steps D, E, F, and G: (R)-(7-Chloro-4,6-difluoro-1H-benzo[d]imidazol-2-yl)(5-methyl-7,8-dihydro-1,6-naphthyridin-6(5H)-yl)methanone was prepared from 3-chloro-4,6-difluoro-2-nitroaniline according to the procedure of Example 80, Steps B, C, D, and E. LC-MS: 363.1 [M+H]⁺. ¹H NMR (400 MHz, DMSO-*d*₆) δ 14.55 – 14.03 (m, 1H), 8.47 – 8.36 (m, 1H), 7.85 – 7.59 (m, 1H), 7.54 – 7.41 (m, 1H), 7.33 – 7.18 (m, 1H), 6.05 – 5.62 (m, 1H), 4.77 – 3.64 (m, 1H), 3.45 – 3.35 (m, 1H), 3.22 – 2.94 (m, 2H), 1.73 – 1.47 (m, 3H).

Example 127: (7-Chloro-1H-benzo[d]imidazol-2-yl)(2-hydroxy-5-methyl-7,8-dihydro-1,6-naphthyridin-6(5H)-yl)methanone

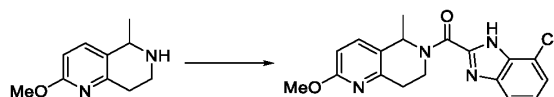


[00511] Step A: A solution of tert-butyl 2-hydroxy-5-methyl-7,8-dihydro-1,6-naphthyridine-6(5H)-carboxylate (65.0 mg, 0.245 mmol) in HCl/MeOH (4M, 2.00 mL) was stirred at 25 °C for 1 h. The mixture was concentrated to give 5-methyl-5,6,7,8-tetrahydro-1,6-naphthyridin-2-ol. LC-MS: 165.3 [M+H]⁺.

[00512] Step B: To a solution of 5-methyl-5,6,7,8-tetrahydro-1,6-naphthyridin-2-ol (55.0 mg, 0.334 mmol), 7-chloro-1H-benzimidazole-2-carboxylic acid (50.0 mg, 0.257 mmol) in DMF (3.00 mL) was added DIEA (100 mg, 0.773 mmol) and HATU (50.0 mg, 0.128 mmol). The mixture was stirred at 25 °C for 2 h. The mixture was filtered and the solid was purified by prep-HPLC (column: Phenomenex luna C18 100 x 40mm x 5um; mobile phase: [H₂O (0.04% HCl)-ACN]; gradient: 20%-50% B over 8.0 min) to give (7-chloro-1H-benzo[d]imidazol-2-yl)(2-

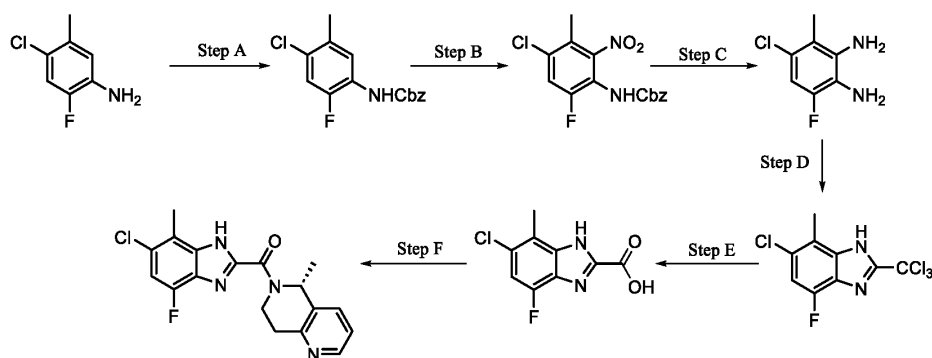
hydroxy-5-methyl-7,8-dihydro-1,6-naphthyridin-6(5H-yl)methanone. LC-MS: 343.1 [M+H]⁺. ¹H NMR (400 MHz, DMSO-*d*₆) δ 7.57 (dd, *J* = 1.1, 7.8 Hz, 1H), 7.50 – 7.27 (m, 3H), 6.30 (br d, *J* = 8.6 Hz, 1H), 5.52 – 5.32 (m, 2H), 3.56 (br d, *J* = 4.6 Hz, 1H), 3.00 – 2.81 (m, 1H), 2.75 – 2.63 (m, 1H), 1.49 (br s, 3H).

Example 128: (7-chloro-1H-benzo[d]imidazol-2-yl)(2-methoxy-5-methyl-7,8-dihydro-1,6-naphthyridin-6(5H)-yl)methanone



[00513] The title compound was prepared from 2-methoxy-5-methyl-5,6,7,8-tetrahydro-1,6-naphthyridine and 4-chloro-1H-benzo[d]imidazole-2-carboxylic acid according to the procedure of Example 1, Step A. LC-MS: 357.1 [M+H]⁺. ¹H NMR (400 MHz, DMSO-*d*₆) δ 7.70 – 7.53 (m, 2H), 7.39 – 7.27 (m, 2H), 6.69 (br d, *J* = 6.8 Hz, 1H), 6.34 – 6.17 (m, 0.5H), 5.75 – 5.28 (m, 1H), 4.80 – 4.65 (m, 0.5H), 3.86 (s, 3H), 3.12 – 3.04 (m, 2H), 2.91 – 2.82 (m, 1H), 1.56 (br s, 3H).

Example 129: (R)-(6-Chloro-4-fluoro-7-methyl-1H-benzo[d]imidazol-2-yl)(5-methyl-7,8-dihydro-1,6-naphthyridin-6(5H)-yl)methanone



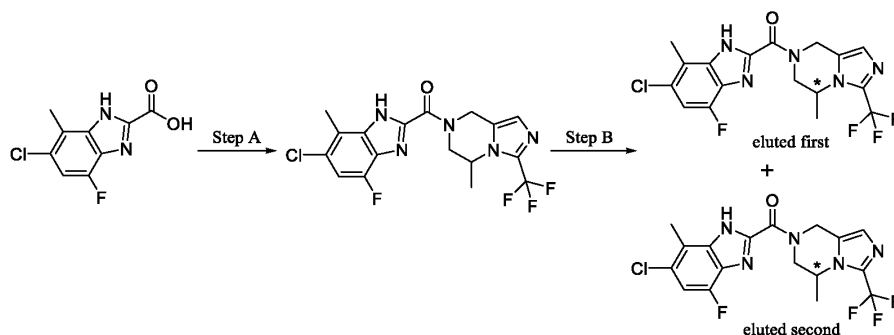
[00514] Step A: 4-Chloro-2-fluoro-5-methylaniline (2.01 g, 12.3 mmol) was dissolved in THF (40.0 mL) at room temperature under nitrogen. K₂CO₃ (3.04 g, 22.0 mmol) and then benzyl chloroformate (2.99 mL, 20.1 mmol) were added. The flask was equipped with a condenser and the mixture was heated at 70 °C for 3 h and allowed to cool down to room temperature. The mixture was adsorbed on silica gel to be purified by flash chromatography on silica gel using a solution of DCM in heptanes (0 to 100% gradient) to give benzyl (4-chloro-2-fluoro-5-methylphenyl)carbamate. ¹H NMR (400 MHz, CDCl₃) δ 8.01 (d, *J* = 7.8 Hz, 1H), 7.44 – 7.32 (m, 5H), 7.08 (d, *J* = 10.6 Hz, 1H), 6.80 (br s, 1H), 5.21 (s, 2H), 2.33 (s, 3H).

[00515] Step B: Benzyl (4-chloro-2-fluoro-5-methylphenyl)carbamate (3.58 g, 12.2 mmol) and ammonium cerium(IV) nitrate (9.77 g, 17.6 mmol) were combined, and benzyl (4-chloro-2-

fluoro-5-methylphenyl)carbamate (3.58 g, 12.2 mmol) was added as a solution in MeCN (25.0 mL) and DCE (25.0 mL) at r. t.. The flask was equipped with a condenser and the mixture was heated at 90 °C overnight. The mixture was filtered on celite using EtOAc. The filtrate was adsorbed on silica to be purified by flash chromatography on silica gel using a solution of EtOAc in heptanes (0 to 100% gradient) to give benzyl (4-chloro-6-fluoro-3-methyl-2-nitrophenyl)carbamate. ¹H NMR (400 MHz, CDCl₃) δ 7.44 – 7.27 (m, 6H), 6.42 (br s, 1H), 5.18 (s, 2H), 2.34 (d, *J* = 1.2 Hz, 3H).

[00516] Steps C, D, E, and F: (R)-((6-Chloro-4-fluoro-7-methyl-1H-benzo[d]imidazol-2-yl)(5-methyl-7,8-dihydro-1,6-naphthyridin-6(5H)-yl)methanone was prepared from benzyl (4-chloro-6-fluoro-3-methyl-2-nitrophenyl)carbamate according to the procedure of Example 42, Steps A, B, C, and D. UPLC-MS: 359.1 [M+H]⁺. ¹H NMR (500 MHz, CD₃CN) δ 8.45 – 8.34 (m, 1H), 7.68 – 7.52 (m, 1H), 7.26 – 7.11 (m, 2H), 6.76 – 4.72 (m, 2H), 3.78 – 3.35 (m, 1H), 3.28 – 2.93 (m, 2H), 2.56 (s, 3H), 1.76 – 1.52 (m, 3H).

Examples 130A and 130B: (R) or (S)-((6-Chloro-4-fluoro-7-methyl-1H-benzo[d]imidazol-2-yl)(5-methyl-3-(trifluoromethyl)-5,6-dihydroimidazo[1,5-a]pyrazin-7(8H)-yl)methanone and (R) or (S)-((6-Chloro-4-fluoro-7-methyl-1H-benzo[d]imidazol-2-yl)(5-methyl-3-(trifluoromethyl)-5,6-dihydroimidazo[1,5-a]pyrazin-7(8H)-yl)methanone

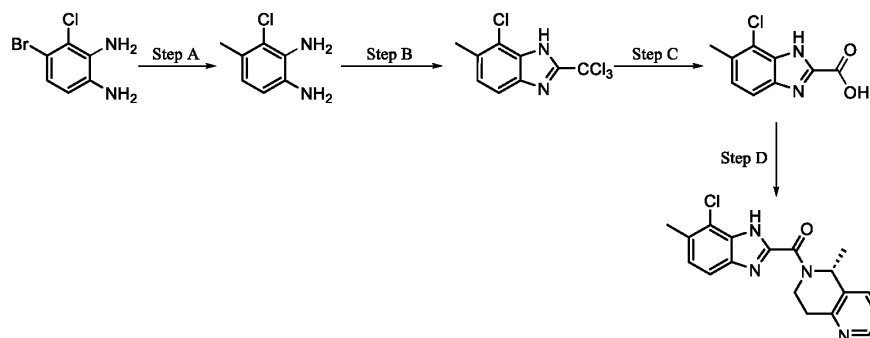


[00517] Step A: Racemic (6-chloro-4-fluoro-7-methyl-1H-benzo[d]imidazol-2-yl)(5-methyl-3-(trifluoromethyl)-5,6-dihydroimidazo[1,5-a]pyrazin-7(8H)-yl)methanone was prepared from 5-methyl-3-(trifluoromethyl)-5,6,7,8-tetrahydroimidazo[1,5-a]pyrazine and 6-chloro-7-methyl-1H-imidazo[4,5-b]pyridine-2-carboxylic acid according to the procedure of Example 1, Step A. LC-MS: 416.2 [M+H]⁺.

[00518] Step B: Racemic (6-chloro-4-fluoro-7-methyl-1H-benzo[d]imidazol-2-yl)(5-methyl-3-(trifluoromethyl)-5,6-dihydroimidazo[1,5-a]pyrazin-7(8H)-yl)methanone (17 mg) was purified by SFC separation (SFC: Autopurification SFC-MS (Fluid Delivery Module, Pump Control Module II, 2767 Injector/Collector, Stack injector Thar, Analytical Prep 2 Oven, Heat

Exchanger, 515 ACD, , 515 MUP, ABPR-20, 2998 PDA, QDa Performance), UV detection: Waters PDA 2998 (198-360nm), MS detection: Waters QDA Performance, ESI (ES (+/-), 100-1200 amu), Eluant B: CO₂, Eluant A: MeOH +0.1% NH₄OH, Column: Phenomenex, Cellulose tris(3-chloro-4-methylphenylcarbamate), Gradient: isocratic 50% B at 10mL/min for 7 minutes to afford a first eluted compound and a second eluted compound. First eluted compound (**Example 130A**): LC-MS: 416.2 [M+H]⁺. ¹H NMR (500 MHz, CD₃CN with D₂O) δ 7.17 (ad, J = 7.9 Hz, 1H), 6.99 (ad, J = 22.1 Hz, 1H), 6.55 – 5.91 (m, 1H), 5.20 (m, 1H), 4.88 – 4.78 (m, 1H), 4.65 (m, 1H), 3.64 (m, 1H), 2.56 (s, 3H), 1.46 (m, 3H). Second eluted compound (**Example 130B**): LC-MS: 416.2 [M+H]⁺. ¹H NMR (500 MHz, CD₃CN with D₂O) δ 7.18 (add, J = 10.4, 2.9 Hz, 1H), 6.99 (ad, J = 18.8 Hz, 1H), 6.28 (m, 1H), 5.20 (m, 1H), 4.89 – 4.80 (m, 1H), 4.66 (m, 1H), 3.64 (m, 1H), 2.56 (s, 3H), 1.46 (add, J = 17.3, 6.6 Hz, 3H). The absolute stereochemistry for the first and second eluted compounds was not determined.

Example 131: (*R*)-(7-chloro-6-methyl-1H-benzo[d]imidazol-2-yl)(5-methyl-7,8-dihydro-1,6-naphthyridin-6(5H)-yl)methanone

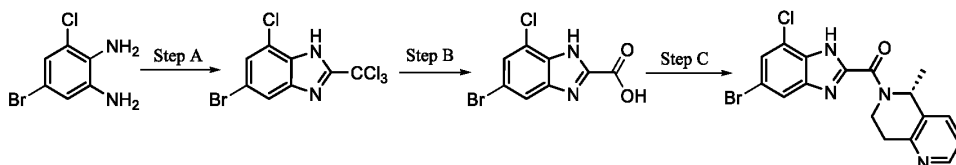


[00519] Step A: A solution of 4-bromo-3-chlorobenzene-1,2-diamine (150 mg, 0.677 mmol) and 1,1'-bis(diphenylphosphino)ferrocene dichloropalladium (II) (24.8 mg, 0.0339 mmol) in 1,4-dioxane (6.90 mL) and water (690 μ L) with cesium carbonate (669 mg, 2.03 mmol) was sparged with nitrogen for 5 min, then added trimethylboroxine (478 μ L, 3.39 mmol) and stirred at 90 °C for 2 h. Cooled to 25 °C and concentrated under reduced pressure, then re-dissolved in EtOAc and diluted with brine. Rinse the organics with brine and dried over anhydrous Na₂SO₄. Filtered and concentrated under reduced pressure with SiO₂ and purified by flash column chromatography on SiO₂ (40 g, 0-100% EtOAc/DCM, 0-2% iPrOH). Concentrated the relevant fractions under reduced pressure to give 3-chloro-4-methylbenzene-1,2-diamine. ¹H NMR (500MHz, CDCl₃) δ 6.57-6.53 (m, 2H), 3.59 (br s, 4H), 2.28 (s, 3H).

[00520] Steps B, C, and D: (*R*)-(7-Chloro-6-methyl-1H-benzo[d]imidazol-2-yl)(5-methyl-7,8-dihydro-1,6-naphthyridin-6(5H)-yl)methanone was prepared from 3-chloro-4-methylbenzene-

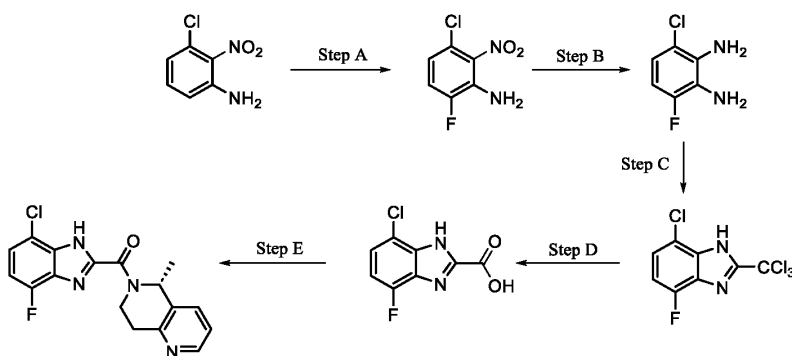
1,2-diamine according to the procedure of Example 35, Steps A, B, and C. LC-MS: 341.2 [M+H]⁺. ¹H NMR (400 MHz, DMSO-d₆) δ 13.38 (br s, 1H), 8.41-8.39 (m, 1H), 7.71 (d, *J* = 7.4 Hz, 1H), 7.44 (br s, 1H), 7.32 – 7.20 (m, 2H), 6.48 (br s, 0.5H), 5.73 (q, *J* = 6.5 Hz, 1H), 4.77 – 4.68 (m, 0.5H), 3.75 – 3.74 (m, 1H), 3.72 – 3.71 (m, 1H), 3.69 – 3.68 (m, 1H), 3.37 – 3.12 (m, 1H), 3.02 – 2.93 (m, 1H), 2.46 (s, 3H), 1.68 (d, *J* = 6.7 Hz, 1H), 1.55 (d, *J* = 6.7 Hz, 2H).

Example 132: (R)-(5-Bromo-7-chloro-1H-benzo[d]imidazol-2-yl)(5-methyl-7,8-dihydro-1,6-naphthyridin-6(5H)-yl)methanone



[00521] (R)-(5-Bromo-7-chloro-1H-benzo[d]imidazol-2-yl)(5-methyl-7,8-dihydro-1,6-naphthyridin-6(5H)-yl)methanone was prepared from 5-bromo-3-chlorobenzene-1,2-diamine according to the procedure of Example 30, Steps A, B, and C. LC-MS: 407.0 [M+H]⁺. ¹H NMR (400 MHz, DMSO-*d*₆) δ 8.45 – 8.36 (m, 1H), 7.78 (d, *J* = 7.7 Hz, 1H), 7.69 (s, 1H), 7.63 – 7.43 (m, 1H), 7.32 – 7.18 (m, 1H), 6.25 – 3.55 (m, 2H), 3.46 – 3.36 (m, 1H), 3.23 – 2.87 (m, 2H), 1.71 – 1.50 (m, 3H).

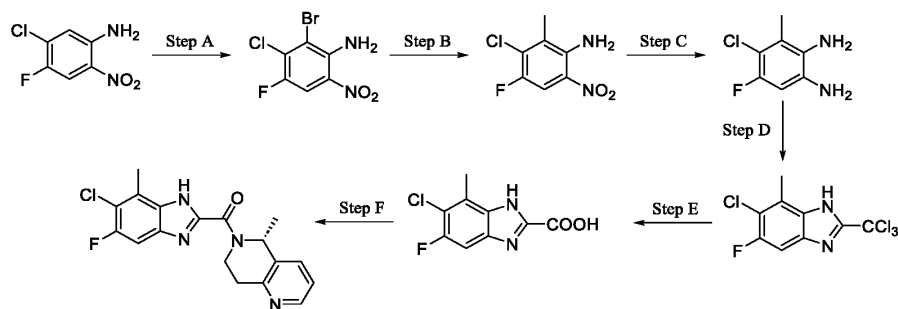
Example 133: (R)-(4-Chloro-7-fluoro-1H-benzo[d]imidazol-2-yl)(5-methyl-7,8-dihydro-1,6-naphthyridin-6(5H)-yl)methanone



[00522] Step A: 3-Chloro-2-nitroaniline (1.00 g, 5.79 mmol) was dissolved in MeCN (40.0 mL) under nitrogen, and SelectFluor (2.14 g, 5.79 mmol) was added. The reaction was heated at 85 °C for 30 min, after which the solvent was removed, and the residue diluted with EtOAc and water. The organic layer was removed, concentrated onto silica, and purified by normal phase chromatography (0 to 100% EtOAc in heptanes, 40 g column) to give 3-chloro-6-fluoro-2-nitroaniline.

[00523] Steps B, C, D, and E: (*R*)-(4-Chloro-7-fluoro-1H-benzo[d]imidazol-2-yl)(5-methyl-7,8-dihydro-1,6-naphthyridin-6(5H)-yl)methanone was prepared from 3-chloro-6-fluoro-2-nitroaniline according to the procedure of Example 42, Steps A, B, C, and D. LC-MS: 345.1 [M+H]⁺. ¹H NMR (500 MHz, CDCl₃) δ 11.33 – 10.75 (m, 1H), 8.55 – 8.43 (m, 1H), 7.64 (d, *J* = 40.7 Hz, 1H), 7.31 – 7.13 (m, 2H), 7.08 – 6.92 (m, 1H), 6.44 – 4.92 (m, 2H), 3.86 – 3.68 (m, 1H), 3.47 – 3.32 (m, 1H), 3.32 – 3.13 (m, 1H), 1.85 – 1.60 (m, 3H).

Example 134: (*R*)-(6-Chloro-5-fluoro-7-methyl-1H-benzo[d]imidazol-2-yl)(5-methyl-7,8-dihydro-1,6-naphthyridin-6(5H)-yl)methanone



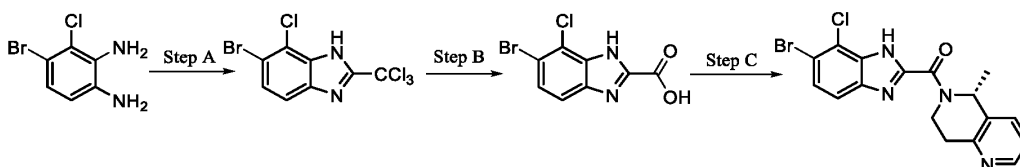
[00524] Step A: 5-Chloro-4-fluoro-2-nitroaniline (500 mg, 2.57 mmol) and *N*-bromosuccinimide (509 mg, 2.83 mmol) were dissolved in DMF (10.0 mL) under nitrogen in a microwave vial and heated at 100°C for 120 minutes. The crude solution was added dropwise to ice-water (~200 mL), and the crude solids collected by vacuum filtration. The solids were taken up in DCM, concentrated onto silica, and purified by normal phase chromatography (0 to 40% EtOAc in heptanes, 40 g) to give 2-bromo-3-chloro-4-fluoro-6-nitroaniline. UPLC-MS: 268.9 [M+H]⁺.

[00525] Step B: 2-Bromo-3-chloro-4-fluoro-6-nitroaniline (456 mg, 1.69 mmol), trimethylboroxine (717 μL, 5.08 mmol), 1,1'-bis(diphenylphosphino)ferrocene dichloropalladium (II) (65.2 mg, 84.6 μmol), and cesium carbonate (1.69 g, 5.08 mmol) were dissolved in nitrogen-sparged water (2.00 mL) and dioxane (18.0 mL), and the mixture was heated at 90 °C for 30 min. The reaction was diluted with ethyl acetate, filtered over Celite®, concentrated onto silica and purified by normal phase chromatography (0 to 100% EtOAc in heptanes, 40 g column) to give 3-chloro-4-fluoro-2-methyl-6-nitroaniline. LC-MS: 203.0 [M+H]⁺.

[00526] Steps C, D, E, and F: (*R*)-(6-Chloro-5-fluoro-7-methyl-1H-benzo[d]imidazol-2-yl)(5-methyl-7,8-dihydro-1,6-naphthyridin-6(5H)-yl)methanone was prepared from 3-chloro-4-fluoro-2-methyl-6-nitroaniline according to the procedure of Example 42, Steps A, B, C, and D. LC-MS: 359.2 [M+H]⁺. ¹H NMR (500 MHz, DMSO-*d*₆) δ 13.71 – 13.11 (m, 1H), 8.49 – 8.34 (m,

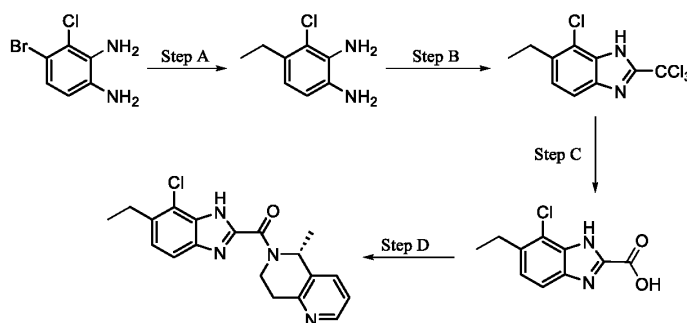
1H), 7.89 – 7.19 (m, 3H), 6.62 – 5.69 (m, 1H), 5.69 – 4.68 (m, 1H), 3.78 – 3.37 (m, 1H), 3.23 – 2.92 (m, 2H), 2.69 – 2.60 (m, 3H), 1.73 – 1.51 (m, 3H).

Example 135: (*R*)-(6-bromo-7-chloro-1*H*-benzo[*d*]imidazol-2-yl)(5-methyl-7,8-dihydro-1,6-naphthyridin-6(5*H*)-yl)methanone



[00527] (*R*)-(6-Bromo-7-chloro-1*H*-benzo[*d*]imidazol-2-yl)(5-methyl-7,8-dihydro-1,6-naphthyridin-6(5*H*)-yl)methanone was prepared from 4-bromo-3-chlorobenzene-1,2-diamine according to the procedure of Example 30, Steps A, B, and C. LC-MS: 405.1/407.1 [M+H]⁺. ¹H NMR (500 MHz, DMSO-*d*₆) δ 8.40 (ddd, *J* = 10.0, 4.6, 1.1 Hz, 1H), 7.80 – 7.59 (m, 2H), 7.50 (dd, *J* = 8.6, 4.5 Hz, 1H), 7.25 (ddd, *J* = 26.0, 7.8, 4.7 Hz, 1H), 6.31 – 5.66 (m, 1H), 5.55 – 4.65 (m, 1H), 3.75 – 3.38 (m, 1H), 3.20 – 2.93 (m, 2H), 1.70 – 1.54 (m, 3H).

Example 136: (*R*)-(7-chloro-6-ethyl-1*H*-benzo[*d*]imidazol-2-yl)(5-methyl-7,8-dihydro-1,6-naphthyridin-6(5*H*)-yl)methanone

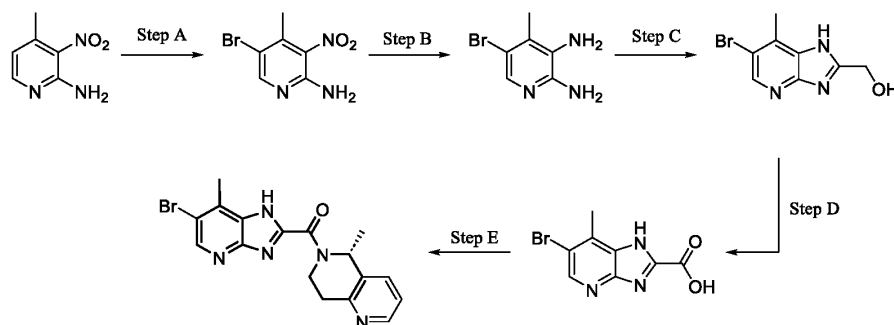


[00528] Step A: A solution of 4-bromo-3-chlorobenzene-1,2-diamine (300 mg, 1.29 mmol) and cesium carbonate (1.27 g, 3.86 mmol) in dioxane (8.82 mL) and water (1.47 mL) with ethylboronic acid (475 mg, 6.43 mmol) was sparged with N₂ for 5 min, then added 1,1'-bis(diphenylphosphino)ferrocene dichloropalladium (II) (94.2 mg, 0.129 mmol) and stirred at 100 °C for 3 h. Cooled to r. t. and concentrated under reduced pressure, then re-dissolved in EtOAc and diluted with brine. Rinse the organics with brine and dried over anhydrous Na₂SO₄. Filtered and concentrated under reduced pressure with SiO₂ and purified by flash column chromatography on SiO₂ (0–100% EtOAc/DCM) to give 3-chloro-4-ethylbenzene-1,2-diamine. LC-MS: 171.0 [M+H]⁺.

[00529] Steps B, C, and D: (*R*)-(7-Chloro-6-ethyl-1*H*-benzo[*d*]imidazol-2-yl)(5-methyl-7,8-dihydro-1,6-naphthyridin-6(5*H*)-yl)methanone was prepared from 3-chloro-4-ethylbenzene-1,2-

diamine according to the procedure of Example 35, Steps A, B, and C. LC-MS: 355.4 $[M+H]^+$. 1H NMR (500 MHz, DMSO- d_6) δ 13.32 (br s, 1H), 8.41 (ddd, $J = 8.8, 4.7, 1.4$ Hz, 1H), 7.71 (ddd, $J = 70.4, 7.9, 1.0$ Hz, 1H), 7.47 (br s, 1H), 7.31 – 7.21 (m, 2H), 5.76 – 4.70 (m, 1H), 3.75 – 3.38 (m, 1H), 3.20 – 3.13 (m, 1H), 3.02 – 2.94 (m, 1H), 2.84 (qd, $J = 7.5, 3.1$ Hz, 2H), 1.62 (dd, $J = 64.8, 6.8$ Hz, 3H), 1.21 (td, $J = 7.5, 2.7$ Hz, 3H).

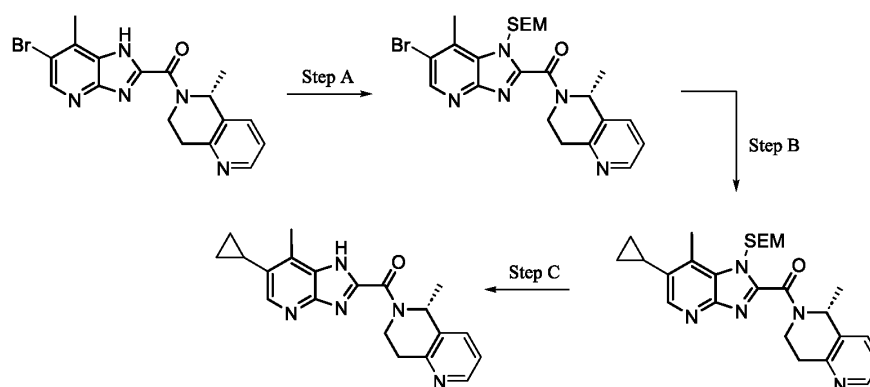
Example 137: (R)-(6-Bromo-7-methyl-1*H*-imidazo[4,5-*b*]pyridin-2-yl)(5-methyl-7,8-dihydro-1,6-naphthyridin-6(5*H*)-yl)methanone



[00530] Step A: To a solution of 2-amino-4-methyl-3-nitropyridine (3.00 g, 19.6 mmol) in AcOH (22.5 mL) under N_2 was added sodium acetate (3.25 g, 39.2 mmol) and stirred vigorously while adding a solution of bromine (1.12 mL, 21.5 mmol) in AcOH (7.5 mL) over 10 min. Stirred for 2 h, then poured slowly into 30 mL of ice water and stirred until all ice melted, then filtered and rinsed the cake with water and dried to give 5-bromo-4-methyl-3-nitropyridin-2-amine. LC-MS: 204.2 $[M+H]^+$.

[00531] Steps B, C, D, and E: (R)-(6-bromo-7-methyl-1*H*-imidazo[4,5-*b*]pyridin-2-yl)(5-methyl-7,8-dihydro-1,6-naphthyridin-6(5*H*)-yl)methanone was prepared from 5-bromo-4-methyl-3-nitropyridin-2-amine according to the procedure of Example 80, Steps B, C, D, and E. LC-MS: 385.8 $[M+H]^+$. 1H NMR (500 MHz, DMSO- d_6) δ 13.81 (brs, 1H), 8.59 – 8.45 (m, 1H), 8.45 – 8.37 (m, 1H), 7.81 – 7.64 (m, 1H), 7.30 – 7.21 (m, 1H), 6.27 – 5.67 (m, 1H), 5.40 – 4.66 (m, 1H), 3.73 – 3.40 (m, 1H), 3.23 – 2.94 (m, 2H), 2.67 – 2.64 (m, 3H), 1.72 – 1.54 (m, 3H).

Example 138: (R)-(6-Cyclopropyl-7-methyl-1*H*-imidazo[4,5-*b*]pyridin-2-yl)(5-methyl-7,8-dihydro-1,6-naphthyridin-6(5*H*)-yl)methanone



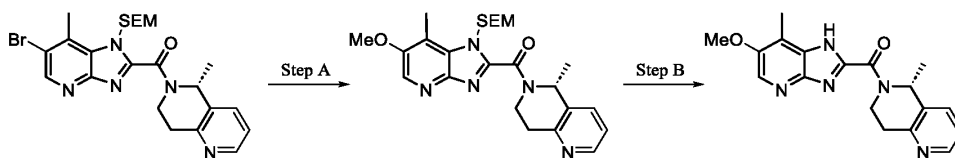
[00532] Step A: To a solution of (R)-(6-bromo-7-methyl-1H-imidazo[4,5-b]pyridin-2-yl)(5-methyl-7,8-dihydro-1,6-naphthyridin-6(5H)-yl)methanone (35.0 mg, 0.0906 mmol) in THF (906 μ L) was added sodium hydride 60% in dispersion in mineral oil (3.26 mg, 0.136 mmol) and the reaction was allowed to stir at 0 °C for 30 min. (2-Chloromethoxyethyl)trimethylsilane (44.5 μ L, 0.227 mmol) was then added dropwise and the reaction was allowed to stir at r. t.. The reaction was quenched with sat. aq. NH_4Cl , and extracted with EtOAc. The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4 , and concentrated. The crude was purified by normal phase chromatography to afford (R)-(6-bromo-7-methyl-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-imidazo[4,5-b]pyridin-2-yl)(5-methyl-7,8-dihydro-1,6-naphthyridin-6(5H)-yl)methanone (mixture of regioisomers). LC-MS: 518.1 $[\text{M}+\text{H}]^+$.

[00533] Step B: A solution of (R)-(6-bromo-7-methyl-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-imidazo[4,5-b]pyridin-2-yl)(5-methyl-7,8-dihydro-1,6-naphthyridin-6(5H)-yl)methanone (10.0 mg, 0.0194 mmol), cyclopropylboronic acid (3.39 mg, 0.0387 mmol), bis(benzonitrile)dichloropalladium(II) (1.49 mg, 0.00387 mmol), SPhos (1.64 mg, 0.00387 mmol), and potassium phosphate tribasic (12.6 mg, 0.0581 mmol) in toluene (387 μ L) was sparged with N_2 gas for 10 min. The reaction was sealed and allowed to stir at 120 °C for 2 h. The reaction was cooled to r. t. and diluted with EtOAc and water. The organic phase was separated and dried over anhydrous Na_2SO_4 , filtered and concentrated to give (R)-(6-cyclopropyl-7-methyl-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-imidazo[4,5-b]pyridin-2-yl)(5-methyl-7,8-dihydro-1,6-naphthyridin-6(5H)-yl)methanone. LC-MS: 478.2 $[\text{M}+\text{H}]^+$.

[00534] Step C: (6-Cyclopropyl-7-methyl-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-imidazo[4,5-b]pyridin-2-yl)(7,8-dihydro-1,6-naphthyridin-6(5H)-yl)methanone (10.0 mg, 0.0209 mmol) was dissolved in DCM (833 μ L) and TFA (81.0 μ L, 1.05 mmol) was added. The reaction was stirred at r.t. for 30 min. The reaction was concentrated, co-evaporated with DCM, re-dissolved in DMSO to be loaded directly onto a C18 column and purified by reverse phase

chromatography (5–100% MeCN/10 mM AmF buffer) to afford (*R*)-(6-cyclopropyl-7-methyl-3*H*-imidazo[4,5-*b*]pyridin-2-yl)(5-methyl-7,8-dihydro-1,6-naphthyridin-6(5*H*)-yl)methanone. LC-MS: 348.2 [M+H]⁺. ¹H NMR (500 MHz, MeOD) δ 8.50 – 8.38 (m, 1H), 8.22 (s, 1H), 7.87 – 7.67 (m, 1H), 7.39 – 7.30 (m, 1H), 5.87 – 5.46 (m, 1H), 4.59 (s, 1H), 3.81 – 3.47 (m, 1H), 3.44 – 3.37 (m, 1H), 3.24 – 3.02 (m, 1H), 2.78 (s, 3H), 2.13 – 2.00 (m, 1H), 1.83 – 1.67 (m, 3H), 1.16 – 1.06 (m, 2H), 0.92 – 0.73 (m, 2H).

Example 139: (*R*)-(6-Methoxy-7-methyl-1*H*-imidazo[4,5-*b*]pyridin-2-yl)(5-methyl-7,8-dihydro-1,6-naphthyridin-6(5*H*)-yl)methanone

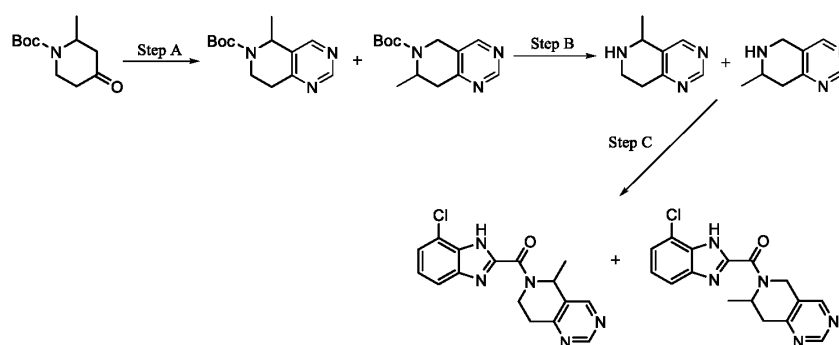


[00535] Step A: A flame-dried tube equipped with a stir bar and sealed with a screw cap was charged with (*R*)-(6-bromo-7-methyl-1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-imidazo[4,5-*b*]pyridin-2-yl)(5-methyl-7,8-dihydro-1,6-naphthyridin-6(5*H*)-yl)methanone (200 mg, 0.387 mmol), *t*BuBrettPhos Pd G3 (33.8 mg, 0.0387 mmol), and sodium *tert*-butoxide (49.9 mg, 0.503 mmol). The reaction tube sealed was evacuated and backfilled with argon. Dioxane (3.87 mL) followed by methanol (79.2 μL, 1.94 mmol) were added via syringe. The screw cap and the teflon septum were wrapped completely with parafilm. The reaction mixture sonicated until there were no visible chunks of NaOtBu. The reaction was stirred at 60 °C for 1 h. The reaction was allowed to cool to room temperature before addition of EtOAc. The reaction slurry was then filtered through a pad of Celite and rinsed with EtOAc. The crude material was concentrated on silica and purified by normal phase chromatography to afford (*R*)-(6-methoxy-7-methyl-1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-imidazo[4,5-*b*]pyridin-2-yl)(5-methyl-7,8-dihydro-1,6-naphthyridin-6(5*H*)-yl)methanone. LC-MS: 469.6 [M+H]⁺.

[00536] Step B: To a solution of (*R*)-(6-methoxy-7-methyl-1-((2-(trimethylsilyl)ethoxy)methyl)-1*H*-imidazo[4,5-*b*]pyridin-2-yl)(5-methyl-7,8-dihydro-1,6-naphthyridin-6(5*H*)-yl)methanone (50.0 mg, 0.107 mmol) in dioxane (1.07 mL) was added TFA (414 μL, 5.35 mmol). The reaction was stirred at 80 °C for 40 h. The reaction was concentrated and co-evaporated with MeCN. The crude was purified by semi-prep HPLC-MS (Column: CSH Prep C18 OBD, 5 μm, 30 x 75 mm. Gradient: isocratic at 10% B for 1 min, 10% to 30% B in 8 min, 30% to 100% B in 0.1 min, hold 100% B for 2.9 min. Eluents: A = Milli Q H₂O + 10 mM AmB pH = 10; B = MeCN. Solvent at 40 °C. Flow: 45 mL/min. Run Time: 12 min). Pure fractions were combined and lyophilized to afford (*R*)-(6-methoxy-7-methyl-1*H*-imidazo[4,5-

b]pyridin-2-yl)(5-methyl-7,8-dihydro-1,6-naphthyridin-6(5*H*)-yl)methanone. LC-MS: 338.4 [M+H]⁺. ¹H NMR (500 MHz, DMSO-*d*₆) δ 8.39 (dd, *J* = 14.6, 4.4 Hz, 1H), 8.18 – 8.06 (m, 1H), 7.79 – 7.54 (m, 1H), 7.28 – 7.17 (m, 1H), 6.30 – 5.65 (m, 1H), 5.33 – 4.66 (m, 1H), 3.88 (s, 3H), 3.61 – 3.51 (m, 1H), 3.20 – 3.12 (m, 1H), 3.03 – 2.86 (m, 2H), 2.43 – 2.34 (m, 3H), 1.66 – 1.51 (m, 3H).

Examples 140A and 140B: (7-Chloro-1H-benzo[d]imidazol-2-yl)(7-methyl-7,8-dihydropyrido[4,3-d]pyrimidin-6(5H)-yl)methanone and (7-chloro-1H-benzo[d]imidazol-2-yl)(5-methyl-7,8-dihydropyrido[4,3-d]pyrimidin-6(5H)-yl)methanone



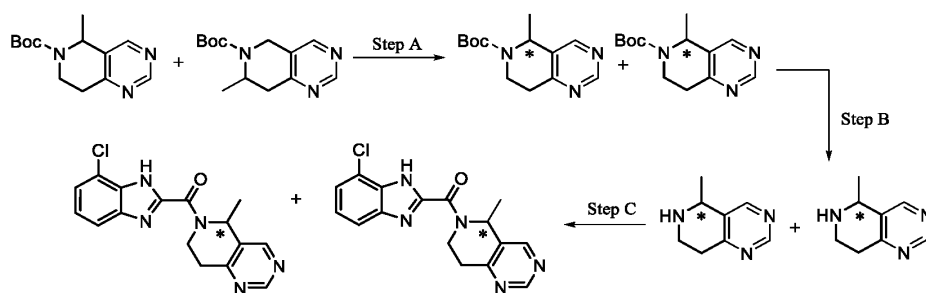
[00537] Step A: To a solution of tert-butyl 2-methyl-4-oxopiperidine-1-carboxylate (1.00 g, 4.55 mmol) in DMF (6.31 mL) was added N,N-dimethylformamide dimethyl acetal (700 μ L, 5.00 mmol) and stirred at 90 °C for 1 h. Concentrated under reduced pressure and re-dissolved in EtOH (7.0 mL), then added formamidine acetate salt (478 mg, 4.55 mmol) followed by a freshly prepared solution of sodium (136 mg, 5.91 mmol) in EtOH (3.0 mL). Stirred the yellow suspension for 10 min before heating at 100 °C for 10 h. Concentrated under reduced pressure and re-partitioned between EtOAc and water and adjusted to pH = 8 with aq. sat. NaHCO₃. Rinse the organics with brine and dried over anhydrous Na₂SO₄. Filtered and concentrated under reduced pressure to give a mixture of tert-butyl 5-methyl-7,8-dihydropyrido[4,3-d]pyrimidine-6(5H)-carboxylate and tert-butyl 7-methyl-7,8-dihydropyrido[4,3-d]pyrimidine-6(5H)-carboxylate. LC-MS: 250.2 [M+H]⁺.

[00538] Step B: To a solution of tert-butyl 5-methyl-7,8-dihydropyrido[4,3-d]pyrimidine-6(5H)-carboxylate (50.0 mg, 0.20 mmol) and tert-butyl 7-methyl-7,8-dihydropyrido[4,3-d]pyrimidine-6(5H)-carboxylate (50.0 mg, 0.20 mmol) in DCM (3.60 mL) was added trifluoroacetic acid (279 μ L, 3.61 mmol) and stirred for 5 min at 25 °C. Concentrated under reduced pressure to give a mixture of 5-methyl-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine and 7-methyl-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine, which was used without further purification. LC-MS: 150.1 [M+H]⁺.

[00539] Step C: To a solution of 5-methyl-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine (29.8 mg, 0.20 mmol) and 7-methyl-5,6,7,8-tetrahydropyrido[4,3-d]pyrimidine (29.8 mg, 0.20 mmol) in DMF (813 μ L) was added 7-chloro-1H-benzo[d]imidazole-2-carboxylic acid (70.4 mg, 0.358 mmol), DIPEA (171 μ L, 0.977 mmol) and HATU (124 mg, 0.326 mmol) and stirred for 5 min at 25 °C. Purified directly by prep-HPLC (Column: CSH Prep C18 OBD, 5 μ m, 30 x 75 mm. Gradient: isocratic at 20% B for 1 min, 15% to 35% B in 8 min, 35% to 100% B in 0.1 min, hold 100% B for 2.9 min. Eluents: A = Milli Q H₂O + 10 mM AmF pH = 3.8; B = MeCN. Solvent at 40 °C. Flow: 45 mL/min. Run Time: 12 min). Lyophilized the first peak to give (7-chloro-1H-benzo[d]imidazol-2-yl)(7-methyl-7,8-dihydropyrido[4,3-d]pyrimidin-6(5H)-yl)methanone. LC-MS: 327.7 [M+H]⁺. ¹H NMR (400MHz, DMSO-*d*₆): δ 13.39 (br s, 1H), 9.01 (s, 1H), 8.76 (s, 1H), 8.63 (s, 0.5H), 8.39 (s, 0.5H), 7.56 (d, *J* = 7.1 Hz, 1H), 7.37 (d, *J* = 7.3 Hz, 1H), 7.31 (t, *J* = 7.8 Hz, 1H), 6.19 – 6.00 (m, 1H), 5.38 (d, *J* = 18.1 Hz, 0.5H), 5.29 – 5.20 (m, 0.5H), 4.85 (d, *J* = 17.5 Hz, 0.5H), 4.49 (d, *J* = 18.6 Hz, 0.5H), 3.43 – 3.37 (m, 0.5H), 3.22 – 3.17 (m, 0.5H), 2.83 (d, *J* = 17.4 Hz, 1H), 1.24 (d, *J* = 6.6 Hz, 3H).

[00540] The mixed fractions were concentrated under reduced pressure, partitioned between EtOAc and sat. aq. NaHCO₃ and the organic dried over anhydrous Na₂SO₄. The mixture was filtered and concentrated under reduced pressure with SiO₂, then was purified by flash column chromatography on SiO₂ (40 g, 0-20% MeOH/DCM). Further purification by prep-HPLC (Column: CSH Prep C18 OBD, 5 μ m, 30 x 75 mm. Gradient: isocratic at 15% B for 1 min, 15% to 35% B in 8 min, 35% to 100% B in 0.1 min, hold 100% B for 2.9 min. Eluents: A = Milli Q H₂O + 10 mM AmF pH = 3.8; B = MeCN. Solvent at 40 °C. Flow: 45 mL/min. Run Time: 12 min) gave (7-chloro-1H-benzo[d]imidazol-2-yl)(5-methyl-7,8-dihydropyrido[4,3-d]pyrimidin-6(5H)-yl)methanone. LC-MS: 328.2 [M+H]⁺. ¹H NMR (400MHz, DMSO-*d*₆): δ 13.51 (br s, 1H), 8.99 (s, 1H), 8.83 (s, 1H), 7.55 (d, *J* = 7.6 Hz, 1H), 7.37 – 7.31 (m, 1H), 7.32 – 7.24 (m, 1H), 6.43 – 6.33 (m, 0.5H), 5.82 (q, *J* = 6.6 Hz, 0.5H), 5.70 – 5.56 (m, 0.5H), 4.73 (dd, *J* = 13.7, 5.1 Hz, 0.5H), 3.75 – 3.64 (m, 0.5H), 3.43 – 3.38 (m, 0.5H), 3.24 – 3.14 (m, 1H), 2.99 – 2.90 (m, 1H), 1.74 (d, *J* = 6.7 Hz, 1H), 1.59 (d, *J* = 6.8 Hz, 2H).

Examples 140C and 140D: (R) or (S)-(7-Chloro-1H-benzo[d]imidazol-2-yl)(5-methyl-7,8-dihydropyrido[4,3-d]pyrimidin-6(5H)-yl)methanone and (R) or (S)-(7-chloro-1H-benzo[d]imidazol-2-yl)(5-methyl-7,8-dihydropyrido[4,3-d]pyrimidin-6(5H)-yl)methanone



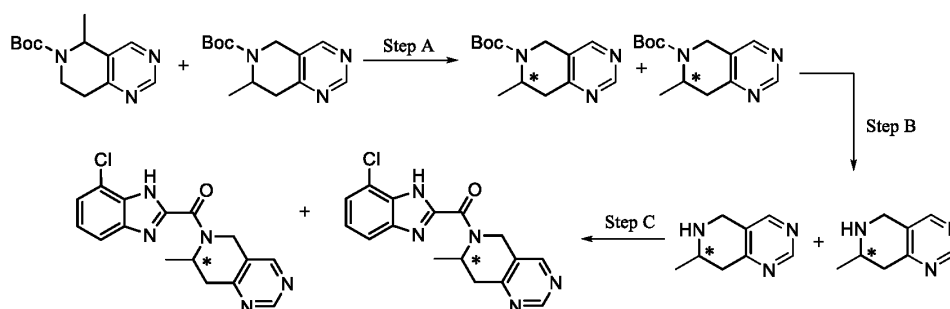
[00541] Step A: A mixture of racemic tert-butyl 5-methyl-7,8-dihydropyrido[4,3-d]pyrimidine-6(5H)-carboxylate and racemic tert-butyl 7-methyl-7,8-dihydropyrido[4,3-d]pyrimidine-6(5H)-carboxylate (Examples 140A/140B, step A) was submitted to chiral separation: LC:

Autopurification LC-MS (2545 Binary, Solvent heater, 2767, SFO, 515, 515, 2998, 3100 MSD Performance), UV detection: Waters PDA 2998 (198-360 nm), MS detection: Waters 3100 MSD Performance, ESI (ES (+), 100-1200 amu), Eluant B: MeCN, Eluant A: AmF 10 mM pH 3.8, Column: Phenomenex, i-Amylose-3, 5 μ m, 10 x 250 mm, Gradient: isocratic 25% B at 4 mL/min for 0.5 min, isocratic 25% B at 4 mL/min to 25% B at 2.5 mL/min, 25% B at 2.5 mL/min to 60% B at 2.5 mL/min for 39 min, hold 60% B at 2.5 mL/min for 2 min, Run time: 42 min). The relevant solution was concentrated and partitioned between EtOAc, and aq. sat. NaHCO₃. The organic phase was washed with brine, dried over anhydrous Na₂SO₄, filtered and concentrated under reduced pressure to give second to elute, tert-butyl 5-methyl-7,8-dihydropyrido[4,3-d]pyrimidine-6(5H)-carboxylate/enantiomer 1 and fourth to elute, tert-butyl 5-methyl-7,8-dihydropyrido[4,3-d]pyrimidine-6(5H)-carboxylate/enantiomer 2. LCMS: 250.3 [M+H]⁺.

[00542] Steps B and C: (7-Chloro-1H-benzo[d]imidazol-2-yl)(2,5-dimethyl-7,8-dihydropyrido[4,3-d]pyrimidin-6(5H)-yl)methanone/enantiomer 1 (**Example 140C**) was prepared from tert-butyl 5-methyl-7,8-dihydropyrido[4,3-d]pyrimidine-6(5H)-carboxylate/enantiomer 1 and (7-chloro-1H-benzo[d]imidazol-2-yl)(2,7-dimethyl-7,8-dihydropyrido[4,3-d]pyrimidin-6(5H)-yl)methanone/enantiomer 2 (**Example 140D**) was prepared from tert-butyl 5-methyl-7,8-dihydropyrido[4,3-d]pyrimidine-6(5H)-carboxylate/enantiomer 2 according to the procedure of Examples 140A and 140B, Steps B, and C. **Example 140C:** LC-MS: 328.5 [M+H]⁺. ¹H NMR (400MHz, DMSO-*d*₆): δ 13.47 (br s, 1H), 8.97 (s, 1H), 8.83 (s, 1H), 7.55 (d, *J* = 7.6 Hz, 1H), 7.37 – 7.31 (m, 1H), 7.32 – 7.24 (m, 1H), 6.43 – 6.33 (m, 0.5H), 5.82 (q, *J* = 6.6 Hz, 0.5H), 5.70 – 5.56 (m, 0.5H), 4.73 (dd, *J* = 13.7, 5.1 Hz, 0.5H), 3.75 – 3.64 (m, 0.5H), 3.43 – 3.38 (m, 0.5H), 3.24 – 3.14 (m, 1H), 2.99 – 2.90 (m, 1H), 1.74 (d, *J* = 6.7 Hz, 1H), 1.59 (d, *J* = 6.8 Hz, 2H). **Example 140D:** LC-MS: 328.5 [M+H]⁺. ¹H NMR (400MHz, DMSO-*d*₆): δ 13.38 (br s, 1H), 8.97 (s, 1H), 8.83 (s, 1H), 7.55 (d, *J* = 7.6

Hz, 1H), 7.37 – 7.31 (m, 1H), 7.32 – 7.24 (m, 1H), 6.43 – 6.33 (m, 0.5H), 5.82 (q, $J = 6.6$ Hz, 0.5H), 5.70 – 5.56 (m, 0.5H), 4.73 (dd, $J = 13.7, 5.1$ Hz, 0.5H), 3.75 – 3.64 (m, 0.5H), 3.43 – 3.38 (m, 0.5H), 3.24 – 3.14 (m, 1H), 2.99 – 2.90 (m, 1H), 1.74 (d, $J = 6.7$ Hz, 1H), 1.59 (d, $J = 6.8$ Hz, 2H). The absolute stereochemistry for the second and fourth eluted compounds was not determined.

Examples 140E and 140F: (R) or (S)-(7-Chloro-1H-benzo[d]imidazol-2-yl)(7-methyl-7,8-dihydropyrido[4,3-d]pyrimidin-6(5H)-yl)methanone and (R) or (S)-(7-Chloro-1H-benzo[d]imidazol-2-yl)(7-methyl-7,8-dihydropyrido[4,3-d]pyrimidin-6(5H)-yl)methanone



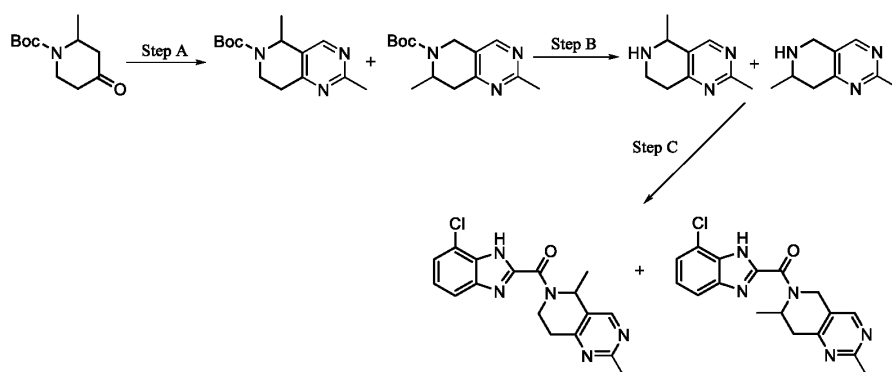
[00543] Step A: A mixture of racemic tert-butyl 5-methyl-7,8-dihydropyrido[4,3-d]pyrimidine-6(5H)-carboxylate and racemic tert-butyl 7-methyl-7,8-dihydropyrido[4,3-d]pyrimidine-6(5H)-carboxylate (Examples 140a/140B, step A) was submitted to chiral separation: LC:

Autopurification LC-MS (2545 Binary, Solvent heater, 2767, SFO, 515, 515, 2998, 3100 MSD Performance), UV detection: Waters PDA 2998 (198-360 nm), MS detection: Waters 3100 MSD Performance, ESI (ES (+), 100-1200 amu), Eluant B: MeCN, Eluant A: AmF 10 mM pH 3.8, Column: Phenomenex, i-Amylose-3, 5 μ m, 10 x 250 mm, Gradient: isocratic 25% B at 4 mL/min for 0.5 min, isocratic 25% B at 4 mL/min to 25% B at 2.5 mL/min, 25% B at 2.5 mL/min to 60% B at 2.5 mL/min for 39 min, hold 60% B at 2.5 mL/min for 2 min, Run time: 42 min). The relevant solution was concentrated and partitioned between EtOAc, and aq. sat. NaHCO₃. Rinse the organics with brine and dried over anhydrous Na₂SO₄. Filtered and concentrated under reduced pressure to give first to elute, tert-butyl 7-methyl-7,8-dihydropyrido[4,3-d]pyrimidine-6(5H)-carboxylate/enantiomer 1 and third to elute, tert-butyl 5-methyl-7,8-dihydropyrido[4,3-d]pyrimidine-6(5H)-carboxylate/enantiomer 2. LCMS: 250.3 [M+H]⁺.

[00544] Steps B and C: (7-Chloro-1H-benzo[d]imidazol-2-yl)(7-methyl-7,8-dihydropyrido[4,3-d]pyrimidin-6(5H)-yl)methanone/enantiomer 1 (**Example 140E**) was prepared from tert-butyl 7-methyl-7,8-dihydropyrido[4,3-d]pyrimidine-6(5H)-carboxylate/enantiomer 1 and (7-(7-chloro-1H-benzo[d]imidazol-2-yl)(7-methyl-7,8-dihydropyrido[4,3-d]pyrimidin-6(5H)-yl)methanone/enantiomer 2 (**Example 140F**) was

prepared from tert-butyl 7-methyl-7,8-dihydropyrido[4,3-d]pyrimidine-6(5H)-carboxylate/enantiomer 2 according to the procedure of Examples 140A and 140B, Steps B, and C. **Example 140E**: LC-MS: 328.3 [M+H]⁺. ¹H NMR (400MHz, DMSO-*d*₆) δ 9.01 (s, 1H), 8.76 (s, 1H), 8.63 (s, 0.5H), 8.44 (s, 0.5H), 7.55 (d, *J* = 7.1 Hz, 1H), 7.36 (d, *J* = 7.3 Hz, 1H), 7.30 (t, *J* = 7.8 Hz, 1H), 6.16 – 6.00 (m, 1H), 5.38 (d, *J* = 18.1 Hz, 0.5H), 5.28 – 5.19 (m, 0.5H), 4.84 (d, *J* = 17.5 Hz, 0.5H), 4.48 (d, *J* = 18.6 Hz, 0.5H), 3.43 – 3.37 (m, 0.5H), 3.22 – 3.17 (m, 0.5H), 2.83 (d, *J* = 17.4 Hz, 1H), 1.24 (d, *J* = 6.6 Hz, 3H). **Example 140F**: LC-MS: 328.5 [M+H]⁺. ¹H NMR (400MHz, DMSO-*d*₆) δ 13.42 (br s, 1H), 9.01 – 8.32 (m, 1H), 8.77 – 8.63 (m, 1H), 7.56 (d, *J* = 7.0 Hz, 1H), 7.38 (d, *J* = 7.6 Hz, 1H), 7.32 (t, *J* = 7.8 Hz, 1H), 6.20 – 6.02 (m, 1H), 5.38 (d, *J* = 18.4 Hz, 0.5H), 5.29 – 5.19 (m, 0.5H), 4.85 (d, *J* = 17.5 Hz, 0.5H), 4.49 (d, *J* = 18.2 Hz, 0.5H), 3.22 – 3.15 (m, 1H), 2.84 (d, *J* = 17.3 Hz, 1H), 1.24 (d, *J* = 6.5 Hz, 3H).

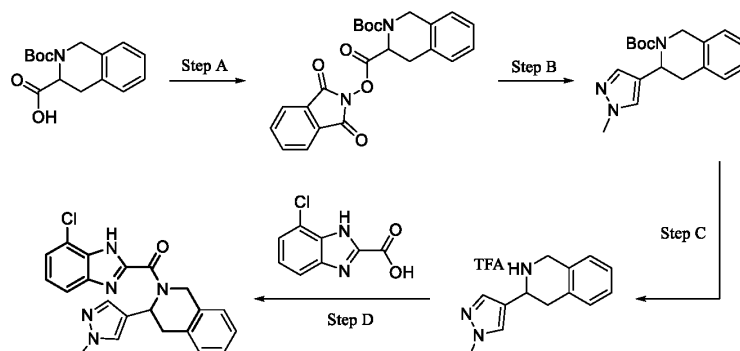
Examples 141A and 141B: (7-Chloro-1H-benzo[d]imidazol-2-yl)(2,5-dimethyl-7,8-dihydropyrido[4,3-d]pyrimidin-6(5H)-yl)methanone and (7-Chloro-1H-benzo[d]imidazol-2-yl)(2,7-dimethyl-7,8-dihydropyrido[4,3-d]pyrimidin-6(5H)-yl)methanone



[00545] Steps A, B, and C: (7-Chloro-1H-benzo[d]imidazol-2-yl)(2,5-dimethyl-7,8-dihydropyrido[4,3-d]pyrimidin-6(5H)-yl)methanone (**Example 141A**) and (7-chloro-1H-benzo[d]imidazol-2-yl)(2,7-dimethyl-7,8-dihydropyrido[4,3-d]pyrimidin-6(5H)-yl)methanone (**Example 141B**) were prepared from tert-butyl 2-methyl-4-oxopiperidine-1-carboxylate and acetamidine hydrochloride according to the procedure of Examples 140A and 140B, Steps A, B, and C. **Example 141A**: LC-MS: 342.2 [M+H]⁺. ¹H NMR (400MHz, DMSO-*d*₆): δ = 13.51 (br s, 1H), 8.99 (s, 1H), 8.83 (s, 1H), 7.55 (d, *J* = 7.6 Hz, 1H), 7.37 – 7.31 (m, 1H), 7.32 – 7.24 (m, 1H), 6.43 – 6.33 (m, 0.5H), 5.82 (q, *J* = 6.6 Hz, 0.5H), 5.70 – 5.56 (m, 0.5H), 4.73 (dd, *J* = 13.7, 5.1 Hz, 0.5H), 3.75 – 3.64 (m, 0.5H), 3.43 – 3.38 (m, 0.5H), 3.24 – 3.14 (m, 1H), 2.99 – 2.90 (m, 1H), 1.74 (d, *J* = 6.7 Hz, 1H), 1.59 (d, *J* = 6.8 Hz, 2H). **Example 141B**: LC-MS: 342.2 [M+H]⁺. ¹H NMR (400MHz, DMSO-*d*₆): δ = 8.59 (s, 1H), 8.46 (s, 1H), 8.34 (s, 1H), 7.51 (d, *J* = 8.0 Hz, 1H), 7.32 (d, *J* = 7.3 Hz, 1H), 7.26 (t, *J* = 7.8 Hz, 1H), 6.09 – 5.95 (m, 1H), 5.28 (d, *J* = 18.3 Hz,

1H), 5.21 – 5.11 (m, 1H), 4.75 (d, $J = 17.4$ Hz, 1H), 4.39 (d, $J = 18.6$ Hz, 1H), 3.16 – 3.08 (m, 1H), 2.73 (d, $J = 17.3$ Hz, 1H), 2.54 (s, 3H), 1.18 (d, $J = 6.7$ Hz, 3H).

Example 142: (7-Chloro-1H-benzo[d]imidazol-2-yl)(3-(1-methyl-1H-pyrazol-4-yl)-3,4-dihydroisoquinolin-2(1H)-yl)methanone



[00546] Step A: A round-bottom flask was charged with 2-(*tert*-butoxycarbonyl)-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid (400 mg, 1.37 mmol), 4-dimethylaminopyridine (16.9 mg, 0.137 mmol) and 2-hydroxyisindolin-1,3-dione (228 mg, 1.37 mmol). DCM (13.7 mL) was added, and the mixture was stirred vigorously. *N,N'*-diisopropylcarbodiimide (237 μ L, 1.51 mmol) was then added dropwise *via* syringe, and the mixture was allowed to stir until the acid was consumed. The mixture was filtered over celite and rinsed with additional DCM/Et₂O. The filtrate was concentrated under reduced pressure, and purification by normal phase chromatography afforded 2-*tert*-butyl 3-(1,3-dioxoisindolin-2-yl) 3,4-dihydroisoquinoline-2,3(1H)-dicarboxylate. LC-MS: 323.1 [M+H]⁺.

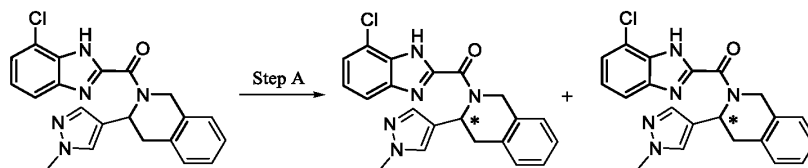
[00547] Step B: A tube containing 2-*tert*-butyl 3-(1,3-dioxoisindolin-2-yl) 3,4-dihydroisoquinoline-2,3(1H)-dicarboxylate (162 mg, 0.385 mmol), 4-iodo-1-methyl-1H-pyrazole (40.0 mg, 0.192 mmol), activated zinc (101 mg, 1.54 mmol), and (2,2'-bipyridine)nickel dichloride (8.33 mg, 0.0288 mmol) was sealed with a rubber septum and electrical tape and evacuated and backfilled with N₂. Then, a solution of chlorotrimethylsilane (0.2 M in DMA, 74.0 μ L, 0.577 mmol) was added and the reaction vessel was placed quickly in an ice bath at 0 °C and left for 2 h. At this time, the reaction was opened to air, diluted with EtOAc, and passed over a plug of celite (eluting with EtOAc). The volatiles were removed under reduced pressure, and the crude material was purified by reverse phase chromatography (10–100% MeCN/10 mM AmF buffer) to afford *tert*-butyl 3-(1-methyl-1H-pyrazol-4-yl)-3,4-dihydroisoquinoline-2(1H)-carboxylate. LC-MS: 314.2 [M+H]⁺.

[00548] Step C: *tert*-Butyl 3-(1-methyl-1H-pyrazol-4-yl)-3,4-dihydroisoquinoline-2(1H)-carboxylate (51.0 mg, 0.163 mmol) was dissolved in DCM (3.25 mL) and TFA (252 μ L, 3.25

mmol) was added. The reaction was allowed to stir at r. t. for 1 h. The reaction was concentrated and co-evaporated with DCM to afford 3-(1-methyl-1H-pyrazol-4-yl)-1,2,3,4-tetrahydroisoquinoline 2,2,2-trifluoroacetate, which was used without further purification. LC-MS: 214.3 [M+H]⁺.

[00549] Step D: (7-Chloro-1*H*-benzo[*d*]imidazol-2-yl)(3-(1-methyl-1*H*-pyrazol-4-yl)-3,4-dihydroisoquinolin-2(1*H*)-yl)methanone was prepared from 3-(1-methyl-1*H*-pyrazol-4-yl)-1,2,3,4-tetrahydroisoquinoline 2,2,2-trifluoroacetate and 7-chloro-1*H*-benzo[*d*]imidazole-2-carboxylic acid according to the procedure of Example 1, Step A. LC-MS: 392.5 [M+H]⁺. ¹H NMR (500 MHz, DMSO-*d*₆) δ 13.45 (br s, 1H), 7.58 – 7.48 (m, 1H), 7.40 – 7.10 (m, 8H), 6.06 – 5.22 (m, 1H), 4.67 – 4.22 (m, 1H), 3.79 – 3.62 (m, 3H), 3.48 – 3.26 (m, 2H), 3.26 – 3.17 (m, 1H).

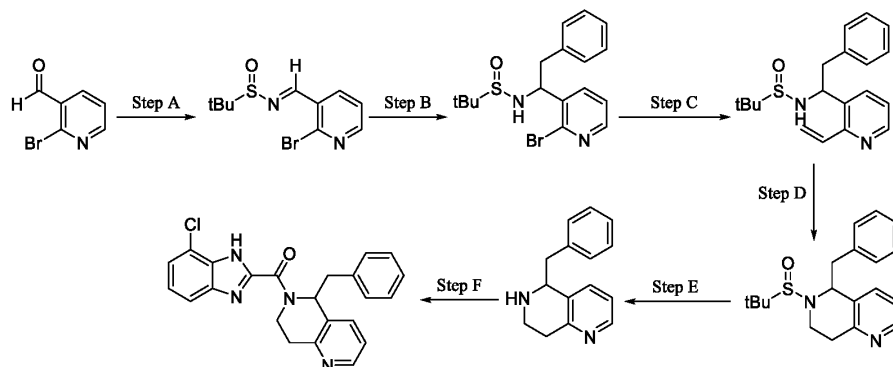
Examples 142A and 142B: (R) or (S)-(7-Chloro-1*H*-benzo[*d*]imidazol-2-yl)(3-(1-methyl-1*H*-pyrazol-4-yl)-3,4-dihydroisoquinolin-2(1*H*)-yl)methanone and (R) or (S)-(7-Chloro-1*H*-benzo[*d*]imidazol-2-yl)(3-(1-methyl-1*H*-pyrazol-4-yl)-3,4-dihydroisoquinolin-2(1*H*)-yl)methanone



[00550] Step A: Racemic (7-chloro-1*H*-benzo[*d*]imidazol-2-yl)(3-(1-methyl-1*H*-pyrazol-4-yl)-3,4-dihydroisoquinolin-2(1*H*)-yl)methanone (45 mg) was separated into its constituent enantiomers (Column Lux Amylose-2 LC, 5 μm, 10 x 250 mm, Pre-Column SecurityGuard cartridge for Lux i-Amy-2, 5 μm, 10 x 10 mm, Manufacturer Phenomenex, Stationary Phase Amylose tris(5-chloro-2-methylphenylcarbamate), Mode Isocratic, Mobile phase 60% ACN/EtOH (1:1) + 0.1% NH₄OH 40% supercritical CO₂, Flow rate 10mL/min, Backpressure 150 bar, Column Temperature 40 °C Run time (min) to afford a first eluted compound and a second eluted compound. First eluted compound (**Example 142A**): LC-MS: 392.6 [M+H]⁺. ¹H NMR (500 MHz, DMSO-*d*₆) δ 13.44 (br s, 1H), 7.62 – 7.52 (m, 1H), 7.49 – 7.37 (m, 2H), 7.34 – 7.30 (m, 1H), 7.29 – 7.17 (m, 4H), 7.15 – 7.10 (m, 1H), 6.07 – 5.20 (m, 1H), 4.67 – 4.23 (m, 1H), 3.74 – 3.65 (m, 3H), 3.46 – 3.32 (m, 2H), 3.24 – 3.18 (m, 1H). Second eluted compound (**Example 142B**): LC-MS: 392.6 [M+H]⁺. ¹H NMR (500 MHz, DMSO-*d*₆) δ 13.54 (br s, 1H), 7.62 – 7.49 (m, 1H), 7.50 – 7.37 (m, 2H), 7.34 – 7.29 (m, 1H), 7.28 – 7.18 (m, 4H), 7.14 – 7.09 (m, 1H), 6.09 – 5.18 (m, 1H), 4.67 – 4.23 (m, 1H), 3.73 – 3.66 (m, 3H), 3.48 – 3.32 (m, 2H),

3.23 – 3.17 (m, 1H). The absolute stereochemistry for the first and second eluted compounds was not determined.

Example 143: (5-Benzyl-7,8-dihydro-1,6-naphthyridin-6(5H)-yl)(7-chloro-1H-benzo[d]imidazol-2-yl)methanone



[00551] Step A: In a 250 mL pressure flask, 2-chloro-3-pyridinecarboxaldehyde (1.00 g, 5.38 mmol) was dissolved in THF (6.0 mL) at room temperature and 2-methyl-2-propanesulfinamide (705 mg, 5.64 mmol) was added. Then, titanium(IV) isopropoxide (3.28 mL, 10.8 mmol) was added as a solution in THF (4.0 mL) to the stirring solution. The flask was sealed and heated at 80 °C overnight. The mixture was allowed to cool to room temperature and water was added. A solid precipitated and was filtered. The solid was rinsed with water and the filtrate was extracted with EtOAc (3 x 25 mL). The combined organic layers were washed with brine (2 x 25 mL), dried over anhydrous Na₂SO₄, filtered and concentrated. The crude material was purified by flash chromatography on silica gel using a solution of EtOAc in heptanes (0 to 100% gradient, 40 g) to give the title compound. UPLC-MS: 289.0 [M+H]⁺.

[00552] Step B: A flame-dried vial under nitrogen at -78 °C was charged with anhydrous and (*E*)-*N*-((2-bromopyridin-3-yl)methylene)-2-methylpropane-2-sulfinamide (160 mg, 0.553 mmol), and benzylmagnesium chloride (493 µL, 0.986 mmol) was added dropwise to solution. The mixture was stirred for 2 h, after which the crude reaction was quenched with saturated aqueous NaHCO₃ solution. The solution was diluted with water and ethyl acetate, the organic layer removed, and the aqueous layer washed again with ethyl acetate. The combined organic layers were dried over anhydrous Na₂SO₄ and concentrated to afford *N*-(1-(2-bromopyridin-3-yl)-2-phenylethyl)-2-methylpropane-2-sulfinamide, which was used without further purification. UPLC-MS: 383.0 [M+H]⁺.

[00553] Step C: *N*-(1-(2-bromopyridin-3-yl)-2-phenylethyl)-2-methylpropane-2-sulfinamide (240 mg, 0.629 mmol), vinylboronic acid pinacol ester (169 µL, 0.944 mmol), cesium carbonate (628 mg, 1.89 mmol) and 1,1'-bis(diphenylphosphino)ferrocene dichloropalladium (II) (51.4 mg,

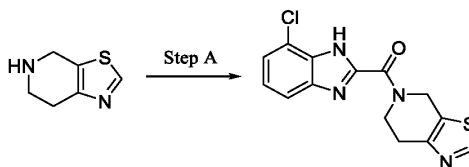
0.0629 mmol) were dissolved in nitrogen-sparged dioxane (10.0 mL) and water (1.00 mL) and heated at 100 °C for 16 h. The reaction was diluted with ethyl acetate, filtered over celite, and concentrated onto silica. The material was purified by flash chromatography (0 to 100% EtOAc in heptanes, with 3% IPA, 40 g column) to afford 2-methyl-N-(2-phenyl-1-(2-vinylpyridin-3-yl)ethyl)propane-2-sulfonamide. UPLC-MS: 329.8 [M+H]⁺.

[00554] Step D: 2-Methyl-N-(2-phenyl-1-(2-vinylpyridin-3-yl)ethyl)propane-2-sulfonamide (81.0 mg, 0.247 mmol) and potassium tert-butoxide (33.2 mg, 0.296 mmol) were added to a flame-dried vessel containing nitrogen-sparged THF (10.0 mL), and the reaction was heated at 70 °C for 16 h. The reaction was concentrated to dryness to afford 5-benzyl-6-(tert-butylsulfinyl)-5,6,7,8-tetrahydro-1,6-naphthyridine, which was used without further purification. UPLC-MS: 225.2 [M+H]⁺.

[00555] Step E: 5-Benzyl-6-(tert-butylsulfinyl)-5,6,7,8-tetrahydro-1,6-naphthyridine (81.0 mg, 0.247 mmol) was taken up in MeOH (2.00 mL), and hydrochloric acid (4 M in dioxane, 152 µL, 0.609 mmol) was added. After stirring for 1 h, the reaction was concentrated, taken up in water and acetonitrile, and loaded on to a C18 column for purification (0 to 25% MeCN in 10 mM AmF over 10 CV, 20 g column). After lyophilization of the relevant fractions, the material was purified again by reverse phase (0 to 100% MeCN in 10 mM AmB, 10 g column). Lyophilization of the relevant fractions afforded 5-benzyl-5,6,7,8-tetrahydro-1,6-naphthyridine. UPLC-MS: 265.0 [M+H]⁺.

[00556] Step F: (5-Benzyl-7,8-dihydro-1,6-naphthyridin-6(5H)-yl)(7-chloro-1H-benzo[d]imidazol-2-yl)methanone was prepared from 5-benzyl-5,6,7,8-tetrahydro-1,6-naphthyridine and 7-chloro-1H-benzo[d]imidazole-2-carboxylic acid according to the procedure of Example 1, Step A. UPLC-MS: 403.3 [M+H]⁺. ¹H NMR (500 MHz, DMSO-*d*₆) δ 8.39 – 8.34 (m, 1H), 7.74 – 6.78 (m, 10H), 6.07 – 4.50 (m, 2H), 3.89 – 3.51 (m, 1H), 3.34 – 3.10 (m, 2H), 3.11 – 2.87 (m, 2H).

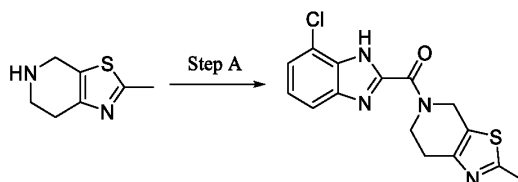
Example 144: (7-Chloro-1H-benzo[d]imidazol-2-yl)(6,7-dihydrothiazolo[5,4-c]pyridin-5(4H)-yl)methanone



[00557] Step A: (7-Chloro-1H-benzimidazol-2-yl)(6,7-dihydrothiazolo[5,4-c]pyridin-5(4H)-yl)methanone was prepared from 7-chloro-1H-benzimidazole-2-carboxylic acid and 4,5,6,7-tetrahydrothiazolo[5,4-c]pyridine hydrochloride according to the procedure of Example

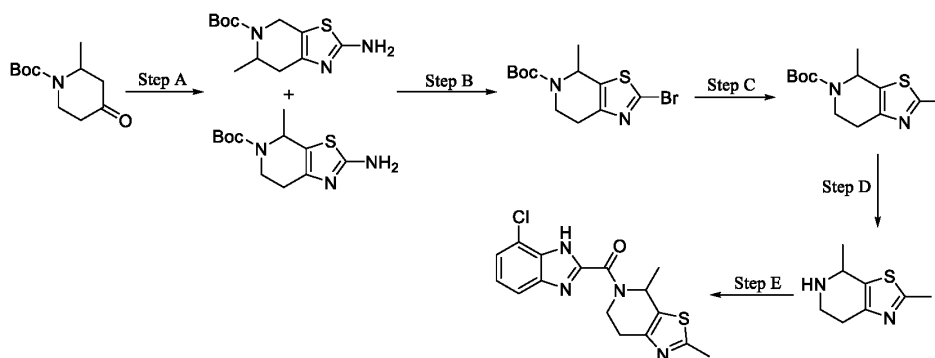
1, Step A. UPLC-MS: 317.3 $[M+H]^+$. 1H NMR (400 MHz, DMSO- d_6) δ 13.47 (br s, 1H), 9.04 – 8.97 (m, 1H), 7.55 (t, $J = 7.4$ Hz, 1H), 7.40 – 7.34 (m, 1H), 7.34 – 7.27 (m, 1H), 5.63 (s, 1H), 5.02 (s, 1H), 4.64 (t, $J = 5.1$ Hz, 1H), 4.07 (t, $J = 5.7$ Hz, 1H), 3.03 (t, $J = 5.6$ Hz, 1H), 2.96 (t, $J = 5.6$ Hz, 1H).

Example 145: (7-Chloro-1H-benzo[d]imidazol-2-yl)(2-methyl-6,7-dihydrothiazolo[5,4-c]pyridin-5(4H)-yl)methanone



[00558] Step A: (7-Chloro-1H-benzo[d]imidazol-2-yl)(2-methyl-6,7-dihydrothiazolo[5,4-c]pyridin-5(4H)-yl)methanone was prepared from 7-chloro-1H-benzo[d]imidazole-2-carboxylic acid and 4,5,6,7-tetrahydro-2-methylthiazolo[5,4-c]pyridine according to the procedure of Example 1, Step A. UPLC-MS: 333.4 $[M+H]^+$. 1H NMR (400 MHz, DMSO- d_6) δ 7.55 (t, $J = 7.0$ Hz, 1H), 7.40 – 7.34 (m, 1H), 7.34 – 7.27 (m, 1H), 5.54 (s, 1H), 4.92 (s, 1H), 4.66 – 4.57 (m, 1H), 4.04 (t, $J = 5.7$ Hz, 1H), 2.96 – 2.83 (m, 2H), 2.66 – 2.55 (m, 3H).

Example 146: (7-Chloro-1H-benzo[d]imidazol-2-yl)(2,4-dimethyl-6,7-dihydrothiazolo[5,4-c]pyridin-5(4H)-yl)methanone



[00559] Step A: A solution of tert-butyl 2-methyl-4-oxopiperidine-1-carboxylate (1.50 g, 7.03 mmol), sulfur powder (451 mg, 1.76 mmol) and cyanamide (597 mg, 14.1 mmol) in pyridine (9.60 mL) was heated for 2 h at 130 °C. Cooled to room temperature, concentrated under reduced pressure and re-dissolved in EtOAc. Rinse the organics with 10% aq. LiCl, brine and dried over anhydrous Na_2SO_4 . Adsorbed the crude material onto SiO_2 and purified by flash column chromatography (0-20% MeOH/DCM + 0.1% NH_3 /MeOH) to afford tert-butyl 2-amino-6-methyl-6,7-dihydrothiazolo[5,4-c]pyridine-5(4H)-carboxylate and tert-butyl 2-amino-4-methyl-6,7-dihydrothiazolo[5,4-c]pyridine-5(4H)-carboxylate.

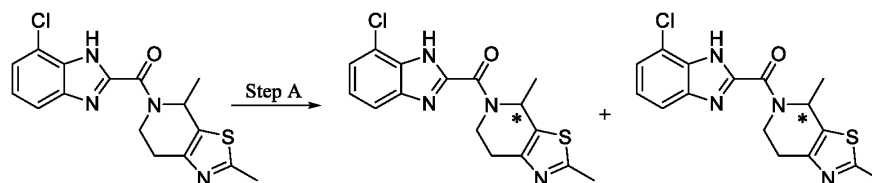
[00560] Step B: To a solution of tert-butyl 2-amino-4-methyl-6,7-dihydrothiazolo[5,4-c]pyridine-5(4H)-carboxylate (614 mg, 2.28 mmol) in MeCN (23.3 mL) at 40 °C was added isopentyl nitrite (383 µL, 2.74 mmol) and stirred for 2 min before adding copper (II) bromide (617 mg, 2.74 mmol) and stirred for 1 h at 40 °C. Concentrated under reduced pressure and redissolved in EtOAc, filtered over Celite® and the filtrate was rinsed with NH₄Cl, brine and dried over anhydrous Na₂SO₄. Adsorbed the crude material onto SiO₂ and purified by flash column chromatography (0-100% EtOAc/hexanes + 0.5% DCM) to provide tert-butyl 2-bromo-4-methyl-6,7-dihydrothiazolo[5,4-c]pyridine-5(4H)-carboxylate. LC-MS: 335.1 [M+H]⁺.

[00561] Step C: A solution of tert-butyl 2-bromo-4-methyl-6,7-dihydrothiazolo[5,4-c]pyridine-5(4H)-carboxylate (250 mg, 0.750 mmol), Trimethylboroxine (318 µL, 2.25 mmol), [1,1'-Bis(diphenylphosphino)ferrocene]dichloropalladium(II), complex with dichloromethane (30.6 mg, 0.0375 mmol) and Cesium carbonate (741 mg, 2.25 mmol) in Dioxane (7.50 mL) and Water (750 µL) was sparged with N₂ for 5 minutes, then heated for 16h at 100 °C. Cooled to room temperature, added another portion of each trimethylboroxine (318 µL, 2.25 mmol) and [1,1'-Bis(diphenylphosphino)ferrocene]dichloropalladium(II), complex with dichloromethane (30.6 mg, 0.0375 mmol) and stirred for 4h at 120 °C. cooled to room temperature, concentrated under reduced pressure and re-partitioned between EtOAc and water. Rinsed with aq. sat. NaHCO₃, brine and dried over anhydrous Na₂SO₄. Adsorbed the crude material onto SiO₂ and purified by flash column chromatography (0-100% EtOAc/heptanes + 0-5% DCM) to give tert-butyl 2,4-dimethyl-6,7-dihydrothiazolo[5,4-c]pyridine-5(4H)-carboxylate. LC-MS: 269.3 [M+H]⁺.

[00562] Step D: To a solution of tert-butyl 2,6-dimethyl-6,7-dihydrothiazolo[5,4-c]pyridine-5(4H)-carboxylate (111 mg, 0.414 mmol) in DCM (4.10 mL) was added trifluoroacetic acid (320 µL, 4.14 mmol) and stirred for 16 h at room temperature. The mixture was concentrated under reduced pressure to 2,4-dimethyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridine, which was used without further purification. UPLC-MS: 169.1 [M+H]⁺.

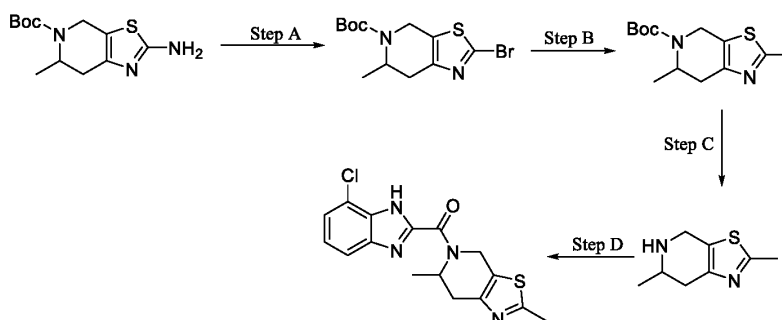
[00563] Step E: (7-Chloro-1H-benzo[d]imidazol-2-yl)(2,4-dimethyl-6,7-dihydrothiazolo[5,4-c]pyridin-5(4H)-yl)methanone was prepared from 2,4-dimethyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridine and 7-chloro-1H-benzo[d]imidazole-2-carboxylic acid according to the procedure of Example 1, Step A. LC-MS: 347.4 [M+H]⁺. ¹H NMR (400 MHz, DMSO-*d*₆) δ 13.43 (br s, 1H), 7.60 – 7.48 (m, 1H), 7.40 – 7.33 (m, 1H), 7.33 – 7.26 (m, 1H), 6.50 – 6.39 (m, 0.5H), 5.81 (q, *J* = 6.4 Hz, 0.5H), 5.71 – 5.51 (m, 0.5H), 4.79 – 4.69 (m, 0.5H), 3.64 – 3.51 (m, 1H), 3.00 – 2.88 (m, 1H), 2.88 – 2.80 (m, 1H), 2.67 – 2.55 (m, 3H), 1.68 (d, *J* = 6.5 Hz, 1H), 1.52 (d, *J* = 6.6 Hz, 2H).

Examples 146A and 146B: (R) or (S)-(7-Chloro-1H-benzo[d]imidazol-2-yl)(2,4-dimethyl-6,7-dihydrothiazolo[5,4-c]pyridin-5(4H)-yl)methanone (enantiomer 1) and (R) or (S)-(7-Chloro-1H-benzo[d]imidazol-2-yl)(2,4-dimethyl-6,7-dihydrothiazolo[5,4-c]pyridin-5(4H)-yl)methanone (enantiomer 2)



[00564] Step A: Racemic (7-chloro-1H-benzo[d]imidazol-2-yl)(2,4-dimethyl-6,7-dihydrothiazolo[5,4-c]pyridin-5(4H)-yl)methanone (52.1 mg) was separated into its constituent enantiomers (LC: Autopurification LC-MS (2545 Binary, Solvent heater, 2767, SFO, 515, 515, 2998, 3100MSD Performance), UV detection: Waters PDA 2998 (198-360nm), MS detection: Acquity QDa Performance, Eluant B: 40% CO₂, Eluant A: 60% MeOH + 0.1% NH₄OH, Column: Lux i-Amylose-1 LC, 5 μm, 10 x 250 mm, Gradient: isocratic, Run time: 13 min) to afford a first eluted compound and a second eluted compound. LC-MS: 347.4 [M+H]⁺. ¹H NMR (400 MHz, DMSO-*d*₆) δ 13.53 (br s, 1H), 7.62 – 7.47 (m, 1H), 7.37 (d, *J* = 7.6 Hz, 1H), 7.34 – 7.27 (m, 1H), 6.59 – 6.40 (m, 0.5H), 5.81 (q, *J* = 6.4 Hz, 0.5H), 5.75 – 5.59 (m, 0.5H), 4.81 – 4.67 (m, 0.5H), 3.62 – 3.53 (m, 1H), 3.00 – 2.89 (m, 1H), 2.89 – 2.77 (m, 1H), 2.64 – 2.57 (m, 3H), 1.68 (d, *J* = 6.5 Hz, 1H), 1.52 (d, *J* = 6.7 Hz, 2H). The absolute stereochemistry for the first and second eluted compounds was not determined.

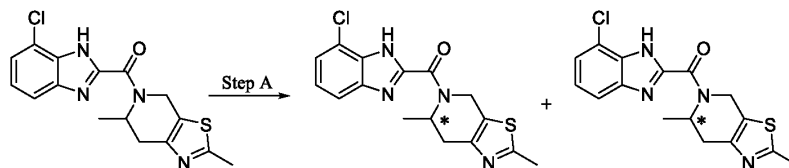
Example 147: (7-Chloro-1H-benzo[d]imidazol-2-yl)(2,6-dimethyl-6,7-dihydrothiazolo[5,4-c]pyridin-5(4H)-yl)methanone



[00565] Steps A, B, C, and D: (7-Chloro-1H-benzo[d]imidazol-2-yl)(2,6-dimethyl-6,7-dihydrothiazolo[5,4-c]pyridin-5(4H)-yl)methanone was prepared from tert-butyl 2-amino-6-methyl-6,7-dihydrothiazolo[5,4-c]pyridine-5(4H)-carboxylate according to the procedure of Example 146, Steps B, C, D, and E. LC-MS: 347.4 [M+H]⁺. ¹H NMR (400 MHz, DMSO-*d*₆) δ 13.09 (br s, 1H), 7.59 – 7.50 (m, 1H), 7.39 – 7.34 (m, 1H), 7.34 – 7.27 (m, 1H), 6.33 – 6.17 (m,

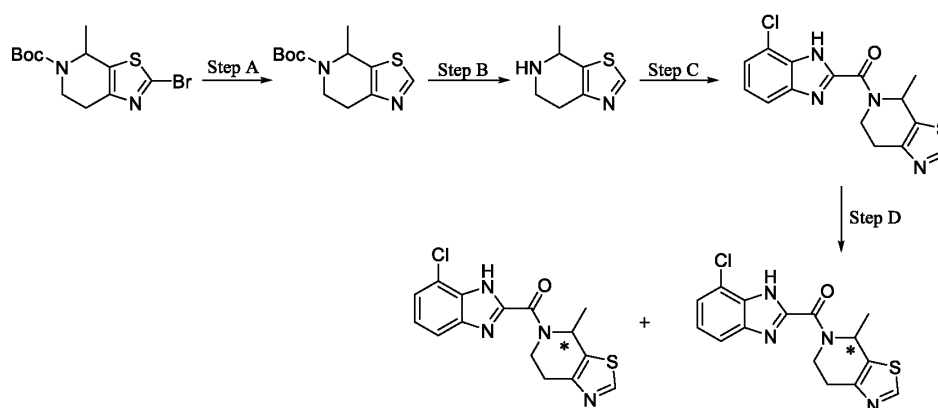
0.5H), 6.05 – 5.91 (m, 0.5H), 5.49 – 5.45 (m, 0.5H), 5.37 – 5.26 (m, 0.5H), 4.68 (d, $J = 17.1$ Hz, 0.5H), 4.32 (d, $J = 17.5$ Hz, 0.5H), 3.16 – 2.98 (m, 1H), 2.78 – 2.69 (m, 1H), 2.62 (d, $J = 7.5$ Hz, 3H), 1.30 – 1.19 (m, 3H).

Examples 147A and 147B: (7-Chloro-1H-benzo[d]imidazol-2-yl)(2,6-dimethyl-6,7-dihydrothiazolo[5,4-c]pyridin-5(4H)-yl)methanone (enantiomer 1) and (7-Chloro-1H-benzo[d]imidazol-2-yl)(2,6-dimethyl-6,7-dihydrothiazolo[5,4-c]pyridin-5(4H)-yl)methanone (enantiomer 2)



[00566] Step A: Racemic(7-chloro-1H-benzo[d]imidazol-2-yl)(2,6-dimethyl-6,7-dihydrothiazolo[5,4-c]pyridin-5(4H)-yl)methanone (35 mg) was separated into its constituent enantiomers (LC: Autopurification LC-MS (2545 Binary, Solvent heater, 2767, SFO, 515, 515, 2998, 3100MSD Performance), UV detection: Waters PDA 2998 (198-360nm), MS detection: Waters 3100MSD Performance, ESI (ES (+), 100-1200 amu), Eluant B: MeCN, Eluant A: 10 mM AMF pH3.8, Column: Phenomenex, i-Amylose-3, 5 μ m, 10 x 250 mm, Gradient: isocratic 99% B at 8mL/min for 15 minutes. Run time: 15 min) to afford a first eluted compound and a second eluted compound. LC-MS: 347.4 $[M+H]^+$. ^1H NMR (400 MHz, DMSO- d_6) δ 13.48 (br s, 1H), 7.59 – 7.48 (m, 1H), 7.35 (d, $J = 7.5$ Hz, 1H), 7.31 – 7.23 (m, 1H), 6.28 – 6.15 (m, 0.5H), 6.03 – 5.86 (m, 0.5H), 5.47 (d, $J = 17.2$ Hz, 0.5H), 5.37 – 5.27 (m, 0.5H), 4.67 (d, $J = 17.5$ Hz, 0.5H), 4.32 (d, $J = 17.7$ Hz, 0.5H), 3.13 – 2.98 (m, 1H), 2.73 (d, $J = 16.4$ Hz, 1H), 2.68 – 2.57 (m, 3H), 1.30 – 1.20 (m, 3H). The absolute stereochemistry for the first and second eluted compounds was not determined.

Examples 148A and 148B: (R) or (S)-(7-Chloro-1H-benzo[d]imidazol-2-yl)(4-methyl-6,7-dihydrothiazolo[4,5-c]pyridin-5(4H)-yl)methanone (enantiomer 1) and (R) or (S)-(7-Chloro-1H-benzo[d]imidazol-2-yl)(4-methyl-6,7-dihydrothiazolo[4,5-c]pyridin-5(4H)-yl)methanone (enantiomer 2)



[00567] Step A: To a flask was added palladium on carbon 10 % loading (84.0 mg, 0.0789 mmol) and vacuum purged, then replaced the atmosphere with N₂. Added trifluoroethanol (4.00 mL) to form a suspension, then tert-butyl 2-bromo-4-methyl-6,7-dihydrothiazolo[5,4-c]pyridine-5(4H)-carboxylate (263 mg, 0.789 mmol) in trifluoroethanol (4.00 mL) and vacuum purged, replacing the atmosphere with H₂. Repeated the purge/refill cycle twice and allowed the mixture to stir for 16 h at 25 °C. Degassed and re-filled with air, then filtered on a PTFE filter (0.45 µm) and concentrated under reduced pressure to provide tert-butyl 4-methyl-6,7-dihydrothiazolo[5,4-c]pyridine-5(4H)-carboxylate. LCMS: 255.1 [M+H]⁺.

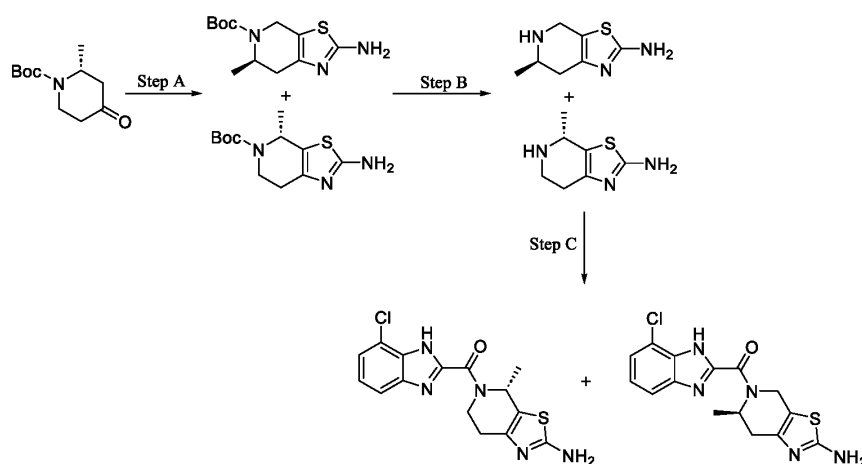
[00568] Step B: To a solution of tert-butyl 4-methyl-6,7-dihydrothiazolo[5,4-c]pyridine-5(4H)-carboxylate (200 mg, 0.786 mmol) in dioxane (4.00 mL) was added hydrochloric acid (4.0 M in dioxane, 1.97 mL, 7.86 mmol) and stirred for 30 min at 25 °C. The mixture was concentrated under reduced pressure to provide 4-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridine, which was used without purification. LCMS: 155.1 [M+H]⁺.

[00569] Step C: 4-Methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridine (109 mg, 0.707 mmol) was dissolved in MeCN (7.12 mL) and aq. sat. NaHCO₃ (3.21 mL, 3.53 mmol) was added until neutral pH. Then, 7-chloro-2-(trichloromethyl)-1H-benzo[d]imidazole (191 mg, 0.707 mmol) was added and the mixture and stirred at 25 °C for 15 min. The mixture was concentrated and partitioned between MeTHF and water. The aqueous layer was extracted with MeTHF once more. The combined organic layers were washed with brine, dried over anhydrous Na₂SO₄, filtered and concentrated. The crude material was purified by flash column chromatography on SiO₂ (40 g, 0-100% EtOAc/heptanes, 0-5% iPrOH) to give (7-chloro-1H-benzo[d]imidazol-2-yl)(4-methyl-6,7-dihydrothiazolo[4,5-c]pyridin-5(4H)-yl)methanone. LCMS: 333.3 [M+H]⁺.

[00570] Step D: Racemic (7-chloro-1H-benzo[d]imidazol-2-yl)(4-methyl-6,7-dihydrothiazolo[4,5-c]pyridin-5(4H)-yl)methanone (60 mg, 0.180 mmol) (60 mg) was separated into its constituent enantiomers by chiral HPLC (LC: Autopurification LC-MS (2545 Binary,

Solvent heater, 2767, SFO, 515, 515, 2998, 3100MSD Performance), UV detection: Waters PDA 2998 (198-360nm), MS detection: Waters 3100MSD Performance, ESI (ES (+), 100-1200 amu), Eluant B: MeCN, Eluant A: 10.0 mM AMF pH3.8, Column: Phenomenex, i-Amylose-3, 5 μ m, 10 x 250 mm, Gradient: isocratic 70% B at 8mL/min for 16 minutes, Run time: 16.0 minutes) to afford a first eluted compound and a second eluted compound. LC-MS: 333.4 [M+H]⁺. ¹H NMR (400 MHz, DMSO-*d*₆) δ 9.02 (s, 1H), 7.59 – 7.52 (m, 1H), 7.39 – 7.33 (m, 1H), 7.33 – 7.26 (m, 1H), 6.55 (q, *J* = 7.1 Hz, 0.4H), 5.92 (q, *J* = 6.4 Hz, 0.6H), 5.66 – 5.56 (m, 0.6H), 4.78 (dd, *J* = 13.3, 4.7 Hz, 0.4H), 3.64 – 3.56 (m, 1H), 3.06 – 2.91 (m, 2H), 1.72 (d, *J* = 6.6 Hz, 1H), 1.55 (d, *J* = 6.7 Hz, 2H). The absolute stereochemistry for the first and second eluted compounds was not determined.

Example 149: (*R*)-(2-Amino-4-methyl-6,7-dihydrothiazolo[5,4-*c*]pyridin-5(4H)-yl)(7-chloro-1H-benzo[d]imidazol-2-yl)methanone



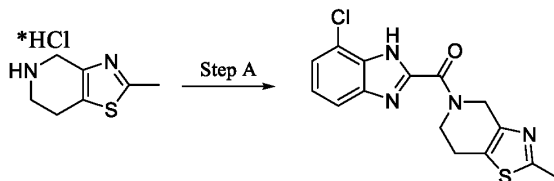
[00571] Step A: A 1:1 mixture of (*R*)-tert-butyl 2-amino-6-methyl-6,7-dihydrothiazolo[5,4-*c*]pyridine-5(4H)-carboxylate and (*R*)-tert-butyl 2-amino-4-methyl-6,7-dihydrothiazolo[5,4-*c*]pyridine-5(4H)-carboxylate was prepared from (*R*)-tert-butyl 2-methyl-4-oxopiperidine-1-carboxylate according to the procedure of Example 146, Step A. LC-MS: 270.3 [M+H]⁺.

[00572] Step B: A 1:1 mixture of (*R*)-6-methyl-4,5,6,7-tetrahydrothiazolo[5,4-*c*]pyridin-2-amine and (*R*)-4-methyl-4,5,6,7-tetrahydrothiazolo[5,4-*c*]pyridin-2-amine was prepared from a 1:1 mixture of (*R*)-tert-butyl 2-amino-6-methyl-6,7-dihydrothiazolo[5,4-*c*]pyridine-5(4H)-carboxylate and (*R*)-tert-butyl 2-amino-4-methyl-6,7-dihydrothiazolo[5,4-*c*]pyridine-5(4H)-carboxylate according to the procedure of Example 146, Step D. LC-MS: 170.1 [M+H]⁺.

[00573] Step C: (*R*)-(2-Amino-4-methyl-6,7-dihydrothiazolo[5,4-*c*]pyridin-5(4H)-yl)(7-chloro-1H-benzo[d]imidazol-2-yl)methanone was prepared from 1:1 mixture of (*R*)-6-methyl-4,5,6,7-tetrahydrothiazolo[5,4-*c*]pyridin-2-amine and (*R*)-4-methyl-4,5,6,7-tetrahydrothiazolo[5,4-

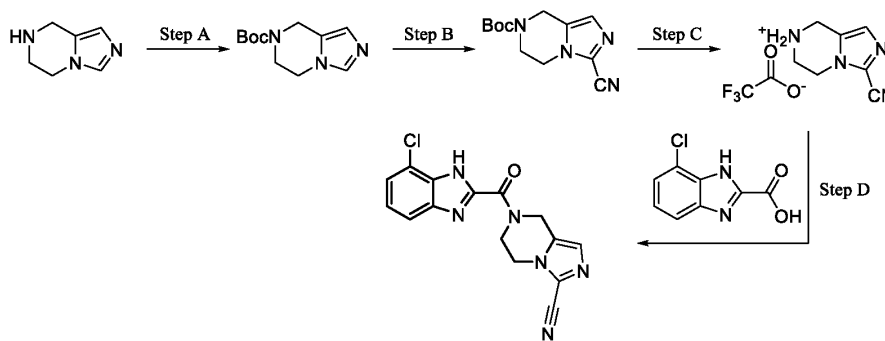
c]pyridin-2-amine according to the procedure of Example 148A and 148B, Step C. LC-MS: 348.6 $[M+H]^+$. 1H NMR (400 MHz, DMSO- d_6) δ 13.48 (br s, 1H), 7.51 (br s, 1H), 7.37 (d, J = 7.6 Hz, 1H), 7.31 (t, J = 7.8 Hz, 1H), 6.87 (s, 2H), 6.24 – 6.16 (m, 0.35H), 5.55 (q, J = 5.6 Hz, 1H), 4.70 – 4.61 (m, 0.55H), 3.59 – 3.51 (m, 1H), 2.77 – 2.65 (m, 1H), 2.60 – 2.52 (m, 2H), 1.60 (d, J = 6.2 Hz, 1H), 1.44 (d, J = 6.5 Hz, 2H).

Example 150: (7-Chloro-1H-benzo[d]imidazol-2-yl)(2-methyl-6,7-dihydrothiazolo[4,5-c]pyridin-5(4H)-yl)methanone



[00574] Step A: (7-Chloro-1H-benzo[d]imidazol-2-yl)(2-methyl-6,7-dihydrothiazolo[4,5-c]pyridin-5(4H)-yl)methanone was prepared from 2-methyl-4,5,6,7-tetrahydrothiazolo[4,5-c]pyridine hydrochloride and 7-chloro-2-(trichloromethyl)-1H-benzo[d]imidazole according to the procedure of Example 148A and 148B, Step C. LC-MS: 333.3 $[M+H]^+$. 1H NMR (400 MHz, DMSO- d_6) δ 13.70 (br s, 0.2H), 13.55 (br s, 0.8H), 7.81 (br s, 0.2H), 7.52 (br s, 0.8H), 7.38 (d, J = 7.5 Hz, 1H), 7.32 (t, J = 7.7 Hz, 1H), 5.60 (s, 0.8H), 5.31 (s, 0.2H), 4.82 (s, 1H), 4.73 – 4.60 (m, 1H), 4.04 (t, J = 5.6 Hz, 1H), 3.05 – 2.97 (m, 1H), 2.95 – 2.87 (m, 1H), 2.62 (d, J = 12.1 Hz, 3H).

Example 151: 7-(7-Chloro-1H-benzo[d]imidazole-2-carbonyl)-5,6,7,8-tetrahydroimidazo[1,5-a]pyrazine-3-carbonitrile



[00575] Step A: *N,N*-Diisopropylethylamine (1.03 mL, 5.85 mmol) and di-*tert*-butyl dicarbonate (1.01 mL, 4.29 mmol) were added to a solution of 5,6,7,8-tetrahydroimidazo[1,5-*a*]pyrazine (500 mg, 3.90 mmol) in DCM (39.0 mL). The reaction mixture was stirred for 45 min at r. t.. The organic phase was washed with aqueous saturated Na_2CO_3 solution, and brine, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The crude product was

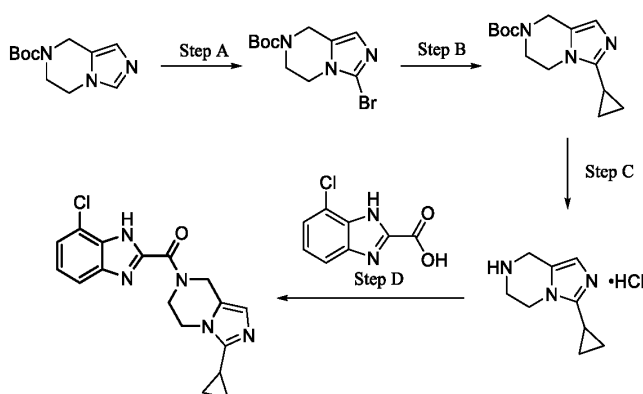
purified by reverse phase chromatography (5–100% MeCN/water) to afford *tert*-butyl 5,6-dihydroimidazo[1,5-*a*]pyrazine-7(8*H*)-carboxylate. LC-MS: 242.2 [M+H]⁺.

[00576] Step B: 4-Dimethylaminopyridine (69.1 mg, 0.560 mmol) and cyanogen bromide (112 µL, 0.560 mmol) in DMF (2.0 mL) under argon at r. t. generated a yellow precipitate of the cyanoaminopyridinium salt to which was added by syringe *tert*-butyl 5,6-dihydroimidazo[1,5-*a*]pyrazine-7(8*H*)-carboxylate (50.0 mg, 0.224 mmol) in DMF (0.5 mL). After 16 h of being stirred, the mixture was poured into aqueous saturated NaHCO₃ solution (10 mL) and extracted with DCM. The organic layers were combined and concentrated. The residue was purified by normal phase chromatography (0–100% EtOAc/DCM) to afford *tert*-butyl 3-cyano-5,6-dihydroimidazo[1,5-*a*]pyrazine-7(8*H*)-carboxylate. LC-MS: 248.0 [M+H]⁺.

[00577] Step C: To a solution of *tert*-butyl 3-cyano-5,6-dihydroimidazo[1,5-*a*]pyrazine-7(8*H*)-carboxylate (34.0 mg, 137.0 µmol) in anhydrous DCM (1.00 mL) was added TFA (106 µL, 1.37 mmol). The reaction was allowed to stir at room temperature for 20 h. The reaction mixture was concentrated and co-evaporated with DCM (2×) to afford 5,6,7,8-tetrahydroimidazo[1,5-*a*]pyrazine-3-carbonitrile 2,2,2-trifluoroacetate, which was used without further purification. LC-MS: 148.5 [M+H]⁺.

[00578] Step D: To a solution of 5,6,7,8-tetrahydroimidazo[1,5-*a*]pyrazine-3-carbonitrile 2,2,2-trifluoroacetate (35.4 mg, 0.135 mmol) and 7-chloro-1*H*-benzo[*d*]imidazole-2-carboxylic acid (29.2 mg, 0.148 mmol) in DMF (1.00 mL) was added *N,N*-diisopropylethylamine (70.9 µL, 0.405 mmol) and HATU (61.6 mg, 0.162 mmol). The reaction was allowed to stir at room temperature for 1 h. The reaction was loaded directly onto a C18 column and purified by reverse phase chromatography (5–100% MeCN/10 mM AmF buffer) to afford 7-(7-chloro-1*H*-benzo[*d*]imidazole-2-carbonyl)-5,6,7,8-tetrahydroimidazo[1,5-*a*]pyrazine-3-carbonitrile. LC-MS: 327.2 [M+H]⁺. ¹H NMR (500 MHz, DMSO-*d*₆) δ 13.60 (br s, 1H), 7.54 (br s, 1H), 7.42 – 7.37 (m, 1H), 7.36 – 7.30 (m, 1H), 7.22 – 7.16 (m, 1H), 5.78 (br s, 1H), 5.02 (s, 1H), 4.92 (br s, 1H), 4.44 (t, *J* = 5.2 Hz, 1H), 4.33 (t, *J* = 5.4 Hz, 1H), 4.17 (t, *J* = 5.5 Hz, 1H).

Example 152: (7-Chloro-1*H*-benzo[*d*]imidazol-2-yl)(3-cyclopropyl-5,6-dihydroimidazo[1,5-*a*]pyrazin-7(8*H*)-yl)methanone



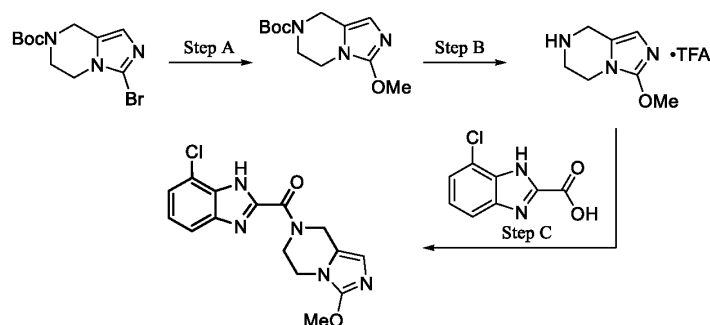
[00579] Step A: *tert*-Butyl 5,6-dihydroimidazo[1,5-*a*]pyrazine-7(8*H*)-carboxylate (200 mg, 0.896 mmol) was dissolved in anhydrous THF (7 mL) under nitrogen atmosphere. The solution was stirred for 1 h at -78°C and *n*-BuLi (448 μL , 1.12 mmol) was added dropwise slowly followed by addition of a solution of carbon tetrabromide (330 mg, 0.985 mmol) in anhydrous THF (3 mL). The reaction was stirred for 1.5 h at -78°C . The reaction was quenched with aq. sat. NH_4Cl solution and diluted with EtOAc. The organic layer was dried over anhydrous Na_2SO_4 and evaporated in vacuo to give the crude product, which was purified by normal phase chromatography (0–100% EtOAc/DCM) to afford *tert*-butyl 3-bromo-5,6-dihydroimidazo[1,5-*a*]pyrazine-7(8*H*)-carboxylate. LC-MS: 303.7 $[\text{M}+\text{H}]^+$.

[00580] Step B: A solution of *tert*-butyl 3-bromo-5,6-dihydroimidazo[1,5-*a*]pyrazine-7(8*H*)-carboxylate (50.0 mg, 0.165 mmol), cyclopropylboronic acid (29.0 mg, 0.331 mmol), bis(benzonitrile)dichloropalladium (II) (6.35 mg, 0.0165 mmol), 2-dicyclohexylphosphino-2',6'-dimethoxybiphenyl (10.5 mg, 0.0248 mmol), and potassium phosphate tribasic (108 mg, 0.496 mmol) in toluene (2.51 mL) was sparged with N_2 gas for 10 min. The reaction was sealed and allowed to stir at 100°C for 2 h. The reaction was cooled to room temperature and diluted with EtOAc and water. The organic phase was separated and dried over anhydrous Na_2SO_4 , filtered and concentrated. The crude was purified by reverse phase chromatography (5–40% MeCN/10 mM AmF buffer) to afford *tert*-butyl 3-cyclopropyl-5,6-dihydroimidazo[1,5-*a*]pyrazine-7(8*H*)-carboxylate. LC-MS: 263.8 $[\text{M}+\text{H}]^+$.

[00581] Step C: To a solution of *tert*-butyl 3-cyclopropyl-5,6-dihydroimidazo[1,5-*a*]pyrazine-7(8*H*)-carboxylate (36.0 mg, 0.137 mmol) in DCM (1.37 mL) was added HCl (4 M in dioxane, 342 μL , 1.37 mmol). The reaction was stirred at room temperature for 1 h. The reaction was concentrated and co-evaporated with DCM twice to afford 3-cyclopropyl-5,6,7,8-tetrahydroimidazo[1,5-*a*]pyrazine hydrochloride, which was used without further purification. LC-MS: 163.6 $[\text{M}+\text{H}]^+$.

[00582] Step D: (7-Chloro-1*H*-benzo[*d*]imidazol-2-yl)(3-cyclopropyl-5,6-dihydroimidazo[1,5-*a*]pyrazin-7(8*H*)-yl)methanone was prepared from 3-cyclopropyl-5,6,7,8-tetrahydroimidazo[1,5-*a*]pyrazine hydrochloride and 7-chloro-1*H*-benzo[*d*]imidazole-2-carboxylic acid according to the procedure of Example 30, Step C. LC-MS: 342.5 [M+H]⁺. ¹H NMR (500 MHz, DMSO-*d*₆) δ 8.21 (s, 1H), 7.59 – 7.51 (m, 1H), 7.40 – 7.36 (m, 1H), 7.35 – 7.30 (m, 1H), 6.66 – 6.56 (m, 1H), 5.60 (br s, 1H), 4.89 (s, 1H), 4.82 (br s, 1H), 4.23 (t, *J* = 5.4 Hz, 1H), 4.20 – 4.09 (m, 2H), 1.97 – 1.89 (m, 1H), 0.89 – 0.84 (m, 2H), 0.81 – 0.75 (m, 2H).

Example 153: (7-Chloro-1*H*-benzo[*d*]imidazol-2-yl)(3-methoxy-5,6-dihydroimidazo[1,5-*a*]pyrazin-7(8*H*)-yl)methanone



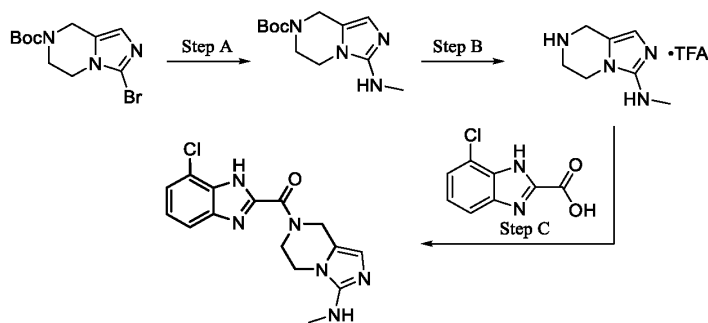
[00583] Step A: A flame-dried tube equipped with a stir bar and sealed with a screw cap was charged with *tert*-butyl 3-bromo-5,6-dihydroimidazo[1,5-*a*]pyrazine-7-carboxylate (75.0 mg, 0.248 mmol), *t*BuBrettPhos Pd G3 (21.6 mg, 0.0248 mmol), and NaO*t*Bu (32.0 mg, 0.323 mmol). The reaction tube sealed was evacuated and backfilled with argon. Methanol (102 μL, 2.48 mmol) followed by dioxane (993 μL) were added via syringe. The screw cap and the teflon septum were wrapped completely with parafilm. The reaction mixture sonicated until there were no visible chunks of NaO*t*Bu. The reaction was stirred at 60 °C for 3 d. The reaction was allowed to cool to room temperature before addition of EtOAc (2 mL). The reaction slurry was then filtered through a pad of celite and rinsed with EtOAc. The crude material was concentrated in vacuo and purified via reverse phase chromatography (5–100% MeCN/10 mM AmF buffer) to afford *tert*-butyl 3-methoxy-5,6-dihydroimidazo[1,5-*a*]pyrazine-7(8*H*)-carboxylate. LC-MS: 254.2 [M+H]⁺.

[00584] Step B: 3-Methoxy-5,6,7,8-tetrahydroimidazo[1,5-*a*]pyrazine 2,2,2-trifluoroacetate was prepared from *tert*-butyl 3-methoxy-5,6-dihydroimidazo[1,5-*a*]pyrazine-7(8*H*)-carboxylate according to the procedure of Example 142, Step C. LC-MS: 153.6 [M+H]⁺.

[00585] Step C: (7-Chloro-1*H*-benzo[*d*]imidazol-2-yl)(3-methoxy-5,6-dihydroimidazo[1,5-*a*]pyrazin-7(8*H*)-yl)methanone was prepared from 3-methoxy-5,6,7,8-tetrahydroimidazo[1,5-*a*]pyrazine 2,2,2-trifluoroacetate and 7-chloro-1*H*-benzo[*d*]imidazole-2-carboxylic acid

according to the procedure of Example 30, Step C. LC-MS: 332.3 $[M+H]^+$. 1H NMR (400 MHz, DMSO- d_6) δ 8.19 (br s, 1H), 7.57 – 7.52 (m, 1H), 7.41 – 7.36 (m, 1H), 7.34 – 7.29 (m, 1H), 6.48 – 6.26 (m, J = 24.2 Hz, 1H), 5.56 (br s, 1H), 4.84 (br s, 1H), 4.75 – 4.70 (m, 1H), 4.09 – 4.03 (m, 1H), 3.93 – 3.89 (m, 4H), 3.87 – 3.82 (m, 1H).

Example 154: (7-Chloro-1H-benzo[d]imidazol-2-yl)(3-(methylamino)-5,6-dihydroimidazo[1,5-a]pyrazin-7(8H)-yl)methanone



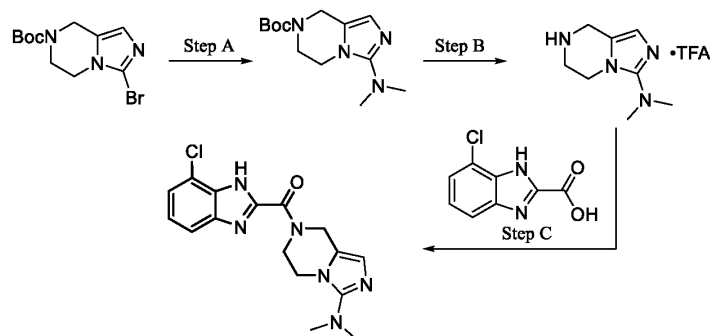
[00586] Step A: To a flame-dried vial, which was equipped with a magnetic stir bar was charged with the *t*BuBrettPhos Pd G3 (28.9 mg, 0.0331 mmol), *t*BuBrettPhos (16.4 mg, 0.0331 mmol), Sodium *tert*-butoxide (65.6 mg, 0.662 mmol), and *tert*-butyl 3-bromo-5,6-dihydroimidazo[1,5-*a*]pyrazine-7(8*H*)-carboxylate (100 mg, 0.331 mmol). The vessel was evacuated and backfilled with argon and then a premixed solution of methylamine (2 M in THF, 1.65 mL, 3.31 mmol) and *t*BuOH (1.32 mL) were added. The vial was sealed and heated to 80 °C for 20 h. The reaction mixture was then diluted with ethyl acetate, washed with sat. aq. NH_4Cl , dried over anhydrous Na_2SO_4 , concentrated *in vacuo*, and purified by reverse phase chromatography (5–100% MeCN/10 mM AmF buffer). Pure fractions were lyophilized to afford *tert*-butyl 3-(methylamino)-5,6-dihydroimidazo[1,5-*a*]pyrazine-7(8*H*)-carboxylate. LC-MS: 252.7 $[M+H]^+$.

[00587] Step B: *N*-Methyl-5,6,7,8-tetrahydroimidazo[1,5-*a*]pyrazin-3-amine 2,2,2-trifluoroacetate was prepared from *tert*-butyl 3-(methylamino)-5,6-dihydroimidazo[1,5-*a*]pyrazine-7(8*H*)-carboxylate according to the procedure of Example 142, Step C. LC-MS: 153.6 $[M+H]^+$.

[00588] Step C: (7-Chloro-1*H*-benzo[d]imidazol-2-yl)(3-(methylamino)-5,6-dihydroimidazo[1,5-*a*]pyrazin-7(8*H*)-yl)methanone was prepared from *N*-methyl-5,6,7,8-tetrahydroimidazo[1,5-*a*]pyrazin-3-amine 2,2,2-trifluoroacetate and 7-chloro-1*H*-benzo[d]imidazole-2-carboxylic acid according to the procedure of Example 30, Step C. LC-MS: 331.4 $[M+H]^+$. 1H NMR (500 MHz, DMSO- d_6) δ 8.17 (br s, 1H), 7.54 (s, 1H), 7.40 – 7.35 (m, 1H), 7.34 – 7.30 (m, 1H), 6.45 – 6.32 (m, 1H), 5.84 (br s, 1H), 5.53 (br s, 1H), 4.81 (s, 1H), 4.72

(br s, 1H), 4.05 (t, $J = 5.6$ Hz, 1H), 3.84 (t, $J = 5.5$ Hz, 1H), 3.78 (t, $J = 5.4$ Hz, 1H), 2.80 – 2.69 (m, 3H).

Example 155: (7-Chloro-1H-benzo[d]imidazol-2-yl)(3-(dimethylamino)-5,6-dihydroimidazo[1,5-a]pyrazin-7(8H)-yl)methanone

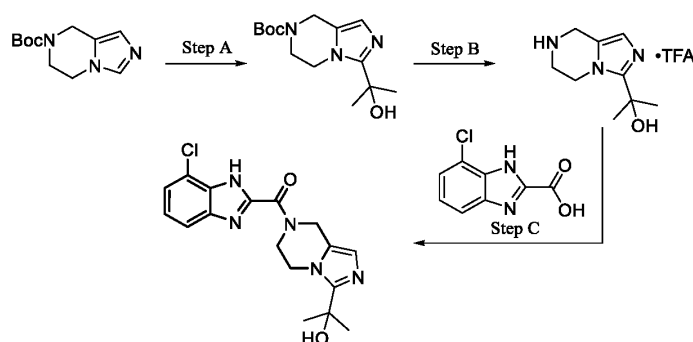


[00589] Step A: *tert*-Butyl 3-(dimethylamino)-5,6-dihydroimidazo[1,5-*a*]pyrazine-7(8H)-carboxylate was prepared from *tert*-butyl 3-bromo-5,6-dihydroimidazo[1,5-*a*]pyrazine-7(8H)-carboxylate and dimethylamine according to the procedure of Example 154, Step A. LC-MS: 266.8 [M+H]⁺.

[00590] Step B: *N,N*-Dimethyl-5,6,7,8-tetrahydroimidazo[1,5-*a*]pyrazin-3-amine 2,2,2-trifluoroacetate was prepared from *tert*-butyl 3-(dimethylamino)-5,6-dihydroimidazo[1,5-*a*]pyrazine-7(8H)-carboxylate according to the procedure of Example 142, Step C. LC-MS: 153.6 [M+H]⁺.

[00591] Step C: (7-Chloro-1H-benzo[d]imidazol-2-yl)(3-(dimethylamino)-5,6-dihydroimidazo[1,5-*a*]pyrazin-7(8H)-yl)methanone was prepared from *N,N*-dimethyl-5,6,7,8-tetrahydroimidazo[1,5-*a*]pyrazin-3-amine 2,2,2-trifluoroacetate and 7-chloro-1H-benzo[d]imidazole-2-carboxylic acid according to the procedure of Example 30, Step C. LC-MS: 334.8 [M+H]⁺. ¹H NMR (500 MHz, D₂O) δ 7.65 (d, $J = 7.8$ Hz, 1H), 7.47 (d, $J = 7.7$ Hz, 1H), 7.40 (t, $J = 7.9$ Hz, 1H), 6.94 – 6.79 (m, 1H), 5.39 (s, 1H), 4.90 (s, 1H), 4.52 – 4.47 (m, 1H), 4.32 – 4.25 (m, 2H), 4.14 (t, $J = 5.0$ Hz, 1H), 3.10 (s, 6H).

Example 156: (7-Chloro-1H-benzo[d]imidazol-2-yl)(3-(2-hydroxypropan-2-yl)-5,6-dihydroimidazo[1,5-*a*]pyrazin-7(8H)-yl)methanone

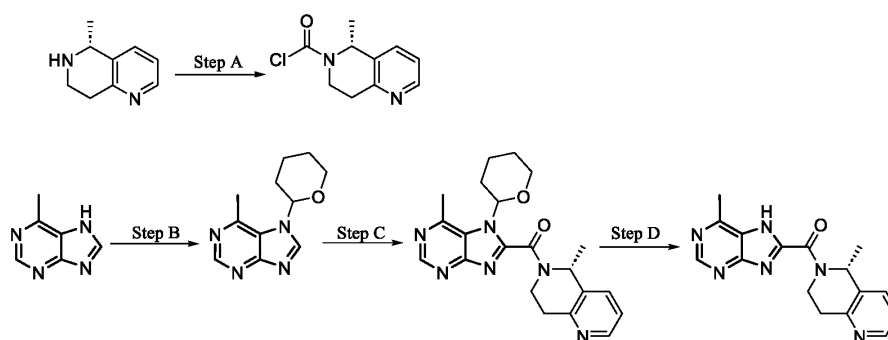


[00592] Step A: *tert*-Butyl 5,6-dihydroimidazo[1,5-*a*]pyrazine-7(8*H*)-carboxylate (0.200 g, 0.896 mmol) was dissolved in anhydrous THF (7 mL) under nitrogen atmosphere and cooled to -78°C . *n*-Butyllithium (2.5 M in hexanes, 537 μL , 1.34 mmol) was added dropwise and the solution was stirred for 1 h at -78°C . A solution of Acetone (105 μL , 1.43 mmol) in anhydrous THF (3 mL) was added dropwise, and the solution was stirred for 2 h at -78°C . The reaction was quenched with aq. sat. NH_4Cl and diluted with EtOAc. The organic layer was dried over anhydrous Na_2SO_4 and evaporated *in vacuo* to give the crude product, which was purified by normal phase chromatography (0–100% EtOAc/DCM) to afford *tert*-butyl 3-(2-hydroxypropan-2-yl)-5,6-dihydroimidazo[1,5-*a*]pyrazine-7(8*H*)-carboxylate. LC-MS: 282.1 $[\text{M}+\text{H}]^+$.

[00593] Step B: 2-(5,6,7,8-Tetrahydroimidazo[1,5-*a*]pyrazin-3-yl)propan-2-ol 2,2,2-trifluoroacetate was prepared from *tert*-butyl 3-(2-hydroxypropan-2-yl)-5,6-dihydroimidazo[1,5-*a*]pyrazine-7(8*H*)-carboxylate according to the procedure of Example 142, Step C. LC-MS: 182.2 $[\text{M}+\text{H}]^+$.

[00594] Step C: (7-Chloro-1*H*-benzo[*d*]imidazol-2-yl)(3-(2-hydroxypropan-2-yl)-5,6-dihydroimidazo[1,5-*a*]pyrazin-7(8*H*)-yl)methanone was prepared from tetrahydroimidazo[1,5-*a*]pyrazin-3-yl)propan-2-ol 2,2,2-trifluoroacetate and 7-chloro-1*H*-benzo[*d*]imidazole-2-carboxylic acid according to the procedure of Example 1, Step A. LC-MS: 360.4 $[\text{M}+\text{H}]^+$. ^1H NMR (500 MHz, $\text{DMSO}-d_6$) δ 8.24 (br s, 1H), 7.56 (d, $J = 7.8$ Hz, 1H), 7.38 (d, $J = 7.6$ Hz, 1H), 7.32 (t, $J = 7.8$ Hz, 1H), 6.66 (d, $J = 29.1$ Hz, 1H), 5.61 (s, 1H), 4.90 (s, 1H), 4.75 – 4.66 (m, 1H), 4.49 – 4.45 (m, 1H), 4.45 – 4.41 (m, 1H), 4.02 (t, $J = 5.1$ Hz, 1H), 1.50 (s, 6H).

Example 157: (R)-(5-Methyl-7,8-dihydro-1,6-naphthyridin-6(5H)-yl)(6-methyl-7H-purin-8-yl)methanone



[00595] Step A: 5-Methyl-5,6,7,8-tetrahydro-1,6-naphthyridine hydrochloride (53.0 mg, 0.287 mmol) and triethylamine (101 μ L, 0.718 mmol) were dissolved in DCM (10.0 mL) at 0 °C, and triphosgene (43.5 mg, 0.144 mmol) was added dropwise as a solution in DCM. The mixture was stirred for 30 min, after which the solution was concentrated to dryness to afford (*R*)-5-methyl-7,8-dihydro-1,6-naphthyridine-6(5H)-carbonyl chloride, which was used without further purification. LC-MS: 211.0 [M+H]⁺.

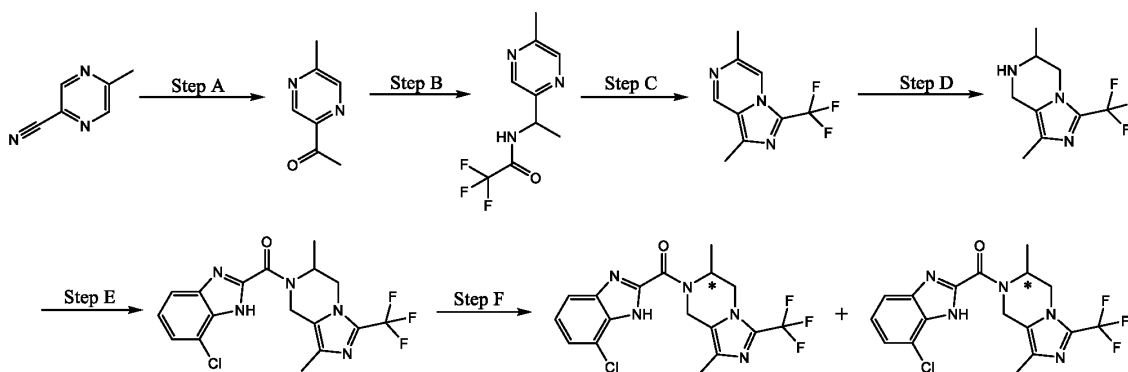
[00596] Step B: 6-Methylpurine (114 μ L, 0.745 mmol), 3,4-dihydro-2H-pyran (210 μ L, 2.24 mmol) and (1*S*)-(+)-camphor-10-sulfonic acid (1.77 mg, 0.00745 mmol) were suspended in ethyl acetate (5.00 mL) and stirred at room temperature for 64 h. The crude reaction was concentrated onto silica and purified by flash chromatography on silica gel using a solution of EtOAc in heptanes (0 to 100% gradient) to afford 6-methyl-9-(tetrahydro-2H-pyran-2-yl)-9H-purine. LC-MS: 219.1 [M+H]⁺.

[00597] Step C: 6-Methyl-9-(tetrahydro-2H-pyran-2-yl)-9H-purine (60.0 mg, 0.275 mmol) was dissolved in THF (5.00 mL) at -78 °C in a flame-dried flask, and lithium diisopropylamide (165 μ L, 0.330 mmol) was added dropwise to solution. The mixture was stirred for 1 h, after which (*R*)-5-methyl-7,8-dihydro-1,6-naphthyridine-6(5H)-carbonyl chloride (57.9 mg, 0.275 mmol) was added dropwise as a solution in THF (1 mL). The mixture was stirred and allowed to reach r. t. over 64 h, after which the reaction was quenched with water and the mixture was concentrated to dryness. The resulting crude material was used without further purification. LC-MS: 393.3 [M+H]⁺.

[00598] Step D: (*R*)-(5-Methyl-7,8-dihydro-1,6-naphthyridin-6(5H)-yl)(6-methyl-7-(tetrahydro-2H-pyran-2-yl)-7H-purin-8-yl)methanone (108 mg, 275.0 μ mol) was suspended in water (5.00 mL), and hydrochloric acid (1M, 2.00 mL, 2.00 mmol) was added. The solution was stirred for 10 min, after which the solution was concentrated to dryness, loaded in DMSO, and filtrated on a 0.45 μ m PTFE filter. The filtrate was purified by semi-prep HPLC-MS (Column: CSH Prep C18 OBD, 5 μ m, 30 x 75 mm. Gradient: isocratic at 15% B for 1 min, 10% to 30 B in 8 min, 35% to

100% B in 0.1 min, hold 100% B for 2.9 min. Eluents: A = Milli Q H₂O + 10 mM AmF pH = 3.8; B = MeCN. Solvent at 40 °C. Flow: 45 mL/min. Run Time: 12 min). The fractions were lyophilized to afford (R)-(5-methyl-7,8-dihydro-1,6-naphthyridin-6(5H)-yl)(6-methyl-7H-purin-8-yl)methanone. LC-MS: 309.2 [M+H]⁺. ¹H NMR (500 MHz, CD₃CN) δ 8.84 (s, 1H), 8.45 – 8.34 (m, 1H), 7.69 – 7.55 (m, 1H), 7.26 – 7.15 (m, 1H), 6.68 – 4.76 (m, 2H), 3.76 – 3.39 (m, 1H), 3.29 – 3.03 (m, 1H), 3.04 – 2.97 (m, 1H), 2.83 – 2.78 (m, 3H), 1.76 – 1.56 (m, 3H).

Examples 157A and 157B: (R) or (S)-(7-Chloro-1H-benzo[d]imidazol-2-yl)(1,6-dimethyl-3-(trifluoromethyl)-5,6-dihydroimidazo[1,5-a]pyrazin-7(8H)-yl)methanone (enantiomer 1) and (R) or (S)-(7-Chloro-1H-benzo[d]imidazol-2-yl)(1,6-dimethyl-3-(trifluoromethyl)-5,6-dihydroimidazo[1,5-a]pyrazin-7(8H)-yl)methanone (enantiomer 2)



[00599] Step A: In a flame-dried flask, 5-methylpyrazine-2-carbonitrile (1.00 g, 7.97 mmol) was added under nitrogen and dissolved in dry Et₂O (50.0 mL) at room temperature. The solution was stirred and cooled to -15 °C (ethylene glycol / CO₂ bath). MeMgI (3.0 M in Et₂O) (3.11 mL, 9.33 mmol) was added dropwise over 1.5 h. Then, the flask was opened and aqueous HCl (1.0 M, 30 mL) was added slowly. After several minutes, the cooling bath was removed so the mixture could warm up to room temperature. The mixture was basified carefully with sat. aq. NaHCO₃ (100 mL) and the layers were separated. The aqueous layer was extracted with MTBE. The combined organic layers were washed with brine, dried over anhydrous Na₂SO₄, filtered and concentrated to give 1-(5-methylpyrazin-2-yl)ethan-1-one. ¹H NMR (500 MHz, CDCl₃) δ 9.11 (d, J = 1.4 Hz, 1H), 8.51 (d, J = 0.9 Hz, 1H), 2.70 (s, 3H), 2.67 (s, 3H).

[00600] Step B: 1-(5-Methylpyrazin-2-yl)ethan-1-one (419 mg, 3.08 mmol) was taken in MeOH (14.0 mL) at room temperature. The mixture was stirred when NH₄OAc (2.40 g, 31.1 mmol) was added. After a few minutes of additional stirring, NaBH₃CN (203 mg, 3.23 mmol) was added in one portion and the mixture was stirred overnight. The mixture was diluted with MeOH and concentrated. The residue was taken in DCM (16.8 mL) at room temperature and DIPEA (2.18 mL, 12.4 mmol) was added. The mixture was stirred and cooled to 0 °C when

TFAA (838 μ L, 5.97 mmol) was added dropwise. The mixture was allowed to stir while the bath warmed up to room temperature over 2 days. Saturated NaHCO_3 was added and the mixture was extracted with EtOAc. The combined organic layers were washed with water, brine, dried over anhydrous Na_2SO_4 , filtered, and concentrated. The crude material was purified by flash chromatography on silica gel using a solution of EtOAc in heptanes (0 to 100% gradient) to give 2,2,2-trifluoro-N-(1-(5-methylpyrazin-2-yl)ethyl)acetamide. LC-MS: 234.2 $[\text{M}+\text{H}]^+$.

[00601] Step C: Phosphorus pentoxide (345 mg, 2.38 mmol) and 2,2,2-trifluoro-N-(1-(5-methylpyrazin-2-yl)ethyl)acetamide (182 mg, 0.780 mmol) were mixed in POCl_3 (7.00 mL) at room temperature. The vial was sealed and the mixture was stirred at 100 $^\circ\text{C}$ overnight. The mixture was allowed to cool down to room temperature and partitioned between EtOAc and water. 5 N NaOH was slowly added to the stirring mixture until the aqueous layer became as colorless as possible. The layers were separated and the aqueous layer (pH = 5-6) was extracted with EtOAc. The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4 , filtered, and concentrated. The crude material was purified by flash chromatography on silica gel using a solution of EtOAc in heptanes (0 to 100% gradient) to give 1,6-dimethyl-3-(trifluoromethyl)imidazo[1,5-a]pyrazine. ^1H NMR (400 MHz, CDCl_3) δ 9.36 (s, 1H), 7.92 (s, 1H), 2.79 (s, 3H), 2.71 (s, 3H).

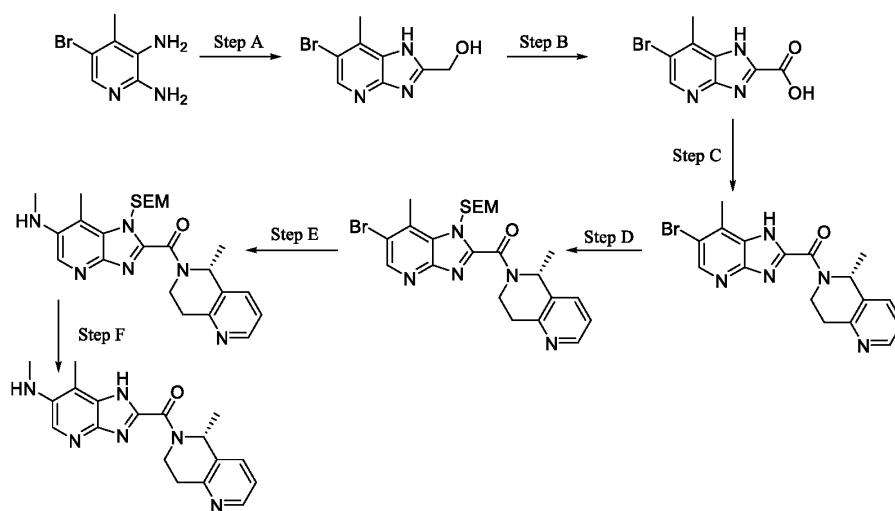
[00602] Step D: 1,6-Dimethyl-3-(trifluoromethyl)imidazo[1,5-a]pyrazine (105 mg, 486.0 μmol) was dissolved in MeOH (4.00 mL) at room temperature. The solution was stirred, evacuated, and refilled with nitrogen. Pd/C (10% wt, 29.0 mg, 0.0273 mmol) was added, the mixture was evacuated and the atmosphere was refilled with nitrogen. The nitrogen balloon was replaced with one of hydrogen. The mixture was evacuated and the atmosphere was refilled with hydrogen. The mixture was stirred under hydrogen for 64 h. The mixture was filtered on celite and the cake was rinsed with MeOH. The filtrate was concentrated to give 1,6-dimethyl-3-(trifluoromethyl)-5,6,7,8-tetrahydroimidazo[1,5-a]pyrazine. LC-MS: 220.3 $[\text{M}+\text{H}]^+$.

[00603] Step E: 1,6-Dimethyl-3-(trifluoromethyl)-5,6,7,8-tetrahydroimidazo[1,5-a]pyrazine (38.7 mg, 0.177 mmol) was taken in DMF (1.50 mL) at room temperature. The mixture was stirred when DIPEA (92.9 μL , 0.528 mmol), 7-chloro-1H-benzo[d]imidazole-2-carboxylic acid (46.2 mg, 0.235 mmol) and HATU (77.2 mg, 0.203 mmol) were added. After 2 h of additional stirring, aqueous NaOH (5 M, 200 μL , 0.999 mmol) was added and the mixture was allowed to stir overnight. The reaction mixture was purified by reverse chromatography on a C-18 column using a solution of MeCN in 10 mM of ammonium formate in water pH = 3.8 (5 to 90% gradient). The tubes with the desired product were combined, concentrated and lyophilized to

give (7-chloro-1H-benzo[d]imidazol-2-yl)(1,6-dimethyl-3-(trifluoromethyl)-5,6-dihydroimidazo[1,5-a]pyrazin-7(8H)-yl)methanone. LC-MS: 398.5 $[M+H]^+$.

Step F: Racemic (7-chloro-1H-benzo[d]imidazol-2-yl)(1,6-dimethyl-3-(trifluoromethyl)-5,6-dihydroimidazo[1,5-a]pyrazin-7(8H)-yl)methanone was separated into its constituent enantiomers by SFC (ChiralPal IG SFC, 5 μ M, 10 x 250, isocratic 60% MeOH + 0.1% NH_4OH + 40% supercritical CO_2 , 10 mL/min, 150 bar, 40 °C, 10 min run, triggered (MS and UV): m/z 397.1 and UV 290 nm) to afford a first eluted compound and second eluted compound. First eluent: LC-MS: 398.2 $[M+H]^+$. ^1H NMR (500 MHz, $\text{DMSO}-d_6$) δ 13.89 – 13.25 (m, 1H), 7.60 – 7.53 (m, 1H), 7.38 (d, $J = 7.5$ Hz, 1H), 7.32 (t, $J = 7.8$ Hz, 1H), 6.40 – 6.08 (m, 1H), 5.25 – 5.00 (m, 1H), 4.58 (d, $J = 17.0$ Hz, 1H), 4.41 – 4.20 (m, 2H), 2.17 (d, $J = 20.4$ Hz, 3H), 1.25 (s, 3H). Second eluent: LC-MS: 398.2 $[M+H]^+$. ^1H NMR (500 MHz, DMSO) δ 13.57 (s, 1H), 7.62 – 7.51 (m, 1H), 7.42 – 7.37 (m, 1H), 7.33 (t, $J = 7.9$ Hz, 1H), 6.46 – 6.03 (m, 1H), 5.23 – 4.99 (m, 1H), 4.58 (d, $J = 17.1$ Hz, 1H), 4.41 – 4.18 (m, 2H), 2.17 (d, $J = 19.2$ Hz, 3H), 1.19 (s, 3H). The absolute stereochemistry for the first and second eluted compounds was not determined.

Example 158: (R)-((7-Methyl-6-(methylamino)-1H-imidazo[4,5-b]pyridin-2-yl)(5-methyl-7,8-dihydro-1,6-naphthyridin-6(5H)-yl)methanone



[00604] Step A: A solution of 5-Bromo-4-methylpyridine-2,3-diamine (3.00 g, 14.1 mmol) in glycolic acid (18.4 mL, 212 mmol) was stirred at 140 °C for 24 h. The reaction was concentrated and stirred in 1 M HCl to break up the thick oil. The mixture was loaded directly onto a C18 column and purified by reverse phase chromatography (5–30% MeCN/10 mM AmF buffer) to give 6-bromo-7-methyl-1H-imidazo[4,5-b]pyridin-2-yl)methanol. LC-MS: 244.1 $[M+H]^+$.

[00605] Step B: To a refluxing solution of potassium permanganate (646 mg, 4.05 mmol) in water (12 mL), a boiling solution of (6-bromo-7-methyl-1H-imidazo[4,5-b]pyridin-2-

yl)methanol (700 mg, 2.89 mmol) and sodium carbonate (460 mg, 4.34 mmol) in water (8 mL) is added. The resulting mixture is heated at reflux for 4 hr. The hot mixture is filtered, the filtrate is cooled to rt, and the pH adjusted to 2 using conc. HCl. The resulting precipitate is collected by vacuum filtration to afford 5-methyl-5,6,7,8-tetrahydro-1,6-naphthyridine hydrochloride. LC-MS: 256.1/258.1 [M+H]⁺.

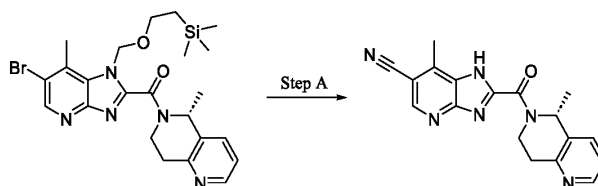
[00606] Step C: To a solution of 5-methyl-5,6,7,8-tetrahydro-1,6-naphthyridine hydrochloride (451 mg, 2.44 mmol) and DIPEA (1.28 mL, 7.32 mmol) in DMF (2.00 mL) was added 6-bromo-7-methyl-1H-imidazo[4,5-b]pyridine-2-carboxylic acid (625 mg, 2.44 mmol) and HATU (1.11 g, 2.93 mmol). The reaction was stirred at rt for 3 h. The reaction was treated with 2 M NaOH for 10 min. The reaction mixture was then loaded directly onto a C18 column and purified by reverse phase chromatography (10–100% MeCN/10 mM AmF buffer). Pure fractions were combined and lyophilized to afford (R)-(6-bromo-7-methyl-1H-imidazo[4,5-b]pyridin-2-yl)(5-methyl-7,8-dihydro-1,6-naphthyridin-6(5H)-yl)methanone. LC-MS: 386.2/388.2 [M+H]⁺.

[00607] Step D: To a solution of (R)-(6-bromo-7-methyl-1H-imidazo[4,5-b]pyridin-2-yl)(5-methyl-7,8-dihydro-1,6-naphthyridin-6(5H)-yl)methanone (860 mg, 2.23 mmol) in THF (22.3 mL) was added sodium hydride (60% in dispersion in mineral oil, 134 mg, 3.34 mmol) and the reaction was allowed to stir at 0 °C for 30 min. (2-Chloromethoxyethyl)trimethylsilane (876 uL, 4.45 mmol) was then added dropwise and the reaction was allowed to stir at rt. The reaction was quenched with sat. NH₄Cl and extracted with EtOAc. The combined organic layers were washed with brine, dried over anhydrous Na₂SO₄, and concentrated. The crude was purified by normal phase chromatography to afford (R)-(6-bromo-7-methyl-3-((2-(trimethylsilyl)ethoxy)methyl)-3H-imidazo[4,5-b]pyridin-2-yl)(5-methyl-7,8-dihydro-1,6-naphthyridin-6(5H)-yl)methanone. LC-MS: 518.3 [M+H]⁺.

[00608] Step E: A flame-dried tube equipped with a magnetic stir bar was charged with tBuBrettPhos Pd G3 (8.44 mg, 0.00968 mmol), t-butylBrettPhos (4.84 mg, 0.00968 mmol), sodium tert-butoxide (19.2 mg, 0.194 mmol), and (R)-(6-bromo-7-methyl-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-imidazo[4,5-b]pyridin-2-yl)(5-methyl-7,8-dihydro-1,6-naphthyridin-6(5H)-yl)methanone (50.0 mg, 0.0968 mmol). The vessel was evacuated and backfilled with argon and then a premixed solution of 2.0 M methylamine solution (484 uL, 0.968 mmol) in THF, and tBuOH (1.45 mL) were added. The vial was sealed heated to 60 °C for 22 h. The reaction mixture was then diluted with ethyl acetate, filtered over a pad of Celite, and concentrated with afford the crude mixture (R)-(7-methyl-6-((methylamino)-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-imidazo[4,5-b]pyridin-2-yl)(5-methyl-7,8-dihydro-1,6-naphthyridin-6(5H)-yl)methanone. LC-MS: 467.5 [M+H]⁺.

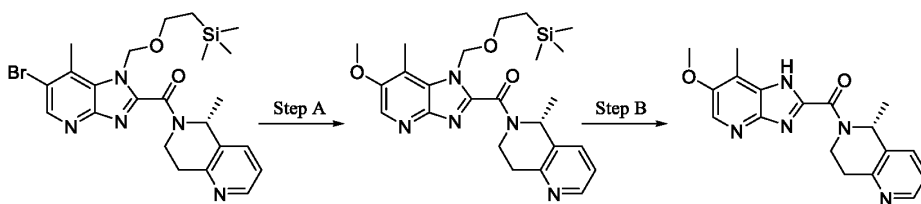
[00609] Step F: To a solution of (R)-(7-methyl-6-(methylamino)-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-imidazo[4,5-b]pyridin-2-yl)(5-methyl-7,8-dihydro-1,6-naphthyridin-6(5H)-yl)methanone (14.0 mg, 30.0 μ mol) in neat TFA (600 μ L) was stirred at rt for 3 h. The reaction was concentrated and co-evaporated with MeCN (2 $\times$). The crude was purified by Prep HPLC (20–40% MeCN/10 mM AmF buffer). Pure fractions were combined and concentrated to afford (R)-(7-Methyl-6-(methylamino)-1H-imidazo[4,5-b]pyridin-2-yl)(5-methyl-7,8-dihydro-1,6-naphthyridin-6(5H)-yl)methanone. LC-MS: 337.4 [M+H]⁺. ¹H NMR (400 MHz, CD₃CN) δ 8.47 – 8.37 (m, 1H), 8.10 – 7.97 (m, 1H), 7.69 – 7.55 (m, 1H), 7.29 – 7.13 (m, 1H), 7.03 – 5.69 (m, 1H), 6.10 – 4.74 (m, 1H), 3.80 – 3.49 (m, 1H), 3.47 – 3.16 (m, 1H), 3.05 – 2.98 (m, 1H), 2.95 (s, 3H), 1.75 – 1.55 (m, 3H). 5 protons overlapping with solvent signal.

Example 159: (R)-7-Methyl-2-(5-methyl-5,6,7,8-tetrahydro-1,6-naphthyridine-6-carbonyl)-1H-imidazo[4,5-b]pyridine-6-carbonitrile



[00610] Step A: A solution of (R)-(6-bromo-7-methyl-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-imidazo[4,5-b]pyridin-2-yl)(5-methyl-7,8-dihydro-1,6-naphthyridin-6(5H)-yl)methanone (25.0 mg, 0.0484 mmol) (product of Example 158, Step D), tris(dibenzylideneacetone)-dipalladium(0) (4.67 mg, 0.00484 mmol), 2-dicyclohexylphosphino-2',4',6'-triisopropylbiphenyl (4.71 mg, 0.00968 mmol), zinc (317 μ g, 0.00484 mmol) and zinc cyanide (6.96 mg, 0.0581 mmol) in DMAc (480 μ L) was sparged with N₂ for 5 minutes, then heated for 30 minutes at 130 °C. Purified directly by reverse phase flash column chromatography (0-100% MeCN/10mM AMF pH3.8). Lyophilized to obtain (R)-7-methyl-2-(5-methyl-5,6,7,8-tetrahydro-1,6-naphthyridine-6-carbonyl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-imidazo[4,5-b]pyridine-6-carbonitrile. LC-MS: 333.3 [M+H]⁺. ¹H NMR (400 MHz, DMSO-d₆) δ 8.76 (app d, 1H), 8.41 (app dd, J = 4.5 Hz, 1H), 7.79 (d, J = 7.4 Hz, 0.6H), 7.64 (d, J = 8.0 Hz, 0.4H), 7.28 (dd, J = 7.7, 4.8 Hz, 0.6H), 7.22 (dd, J = 7.5, 4.8 Hz, 0.4H), 6.17 – 6.06 (m, 0.4H), 5.76 – 5.67 (m, 0.6H), 5.24 – 5.11 (m, 0.6H), 4.77 – 4.66 (m, 0.4H), 3.74 – 3.65 (m, 0.6H), 3.50 – 3.43 (m, 0.4H), 3.24 – 3.12 (m, 1H), 3.02 – 2.97 (m, 1H), 2.95 – 2.73 (m, 3H), 1.70 (d, J = 6.6 Hz, 1H), 1.57 (d, J = 6.6 Hz, 2H).

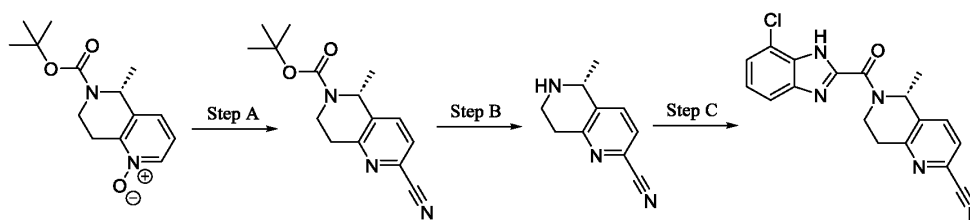
Example 160: (R)-(6-Methoxy-7-methyl-1H-imidazo[4,5-b]pyridin-2-yl)(5-methyl-7,8-dihydro-1,6-naphthyridin-6(5H)-yl)methanone



[00611] Step A: A flame-dried tube equipped with a stir bar and sealed with a screw cap was charged with (R)-(6-bromo-7-methyl-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-imidazo[4,5-b]pyridin-2-yl)(5-methyl-7,8-dihydro-1,6-naphthyridin-6(5H)-yl)methanone (200 mg, 0.387 mmol) (product of Example 158, Step D), tBuBrettPhos Pd G3 (33.8 mg, 0.0387 mmol), and sodium tert-butoxide (49.9 mg, 0.503 mmol). The reaction tube sealed was evacuated and backfilled with argon (3×). Dioxane (3.87 mL) followed by methanol (79.2 uL, 1.94 mmol) were added via syringe. The screw cap and the teflon septum were wrapped completely with parafilm. The reaction mixture was sonicated until there were no visible chunks of NaOtBu. The reaction was stirred at 60 °C for 1 h. The reaction mixture was allowed to cool to rt before addition of EtOAc (2 mL). The reaction slurry was then filtered through a pad of Celite and rinsed with EtOAc. The crude material was concentrated on silica and purified by normal phase chromatography to afford (R)-(6-methoxy-7-methyl-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-imidazo[4,5-b]pyridin-2-yl)(5-methyl-7,8-dihydro-1,6-naphthyridin-6(5H)-yl)methanone. LC-MS: 468.6 [M+H]⁺.

[00612] Step B: To a solution of (R)-(6-methoxy-7-methyl-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-imidazo[4,5-b]pyridin-2-yl)(5-methyl-7,8-dihydro-1,6-naphthyridin-6(5H)-yl)methanone (50.0 mg, 0.107 mmol) in dioxane (1.07 mL) was added TFA (414 uL, 5.35 mmol). The reaction was stirred at 80 °C for 40 h. The reaction mixture was concentrated and co-evaporated with MeCN. The crude was purified by prep-HPLC (10–30% MeCN/10 mM AmB buffer). Pure fractions were combined and lyophilized to afford (R)-(6-methoxy-7-methyl-1H-imidazo[4,5-b]pyridin-2-yl)(5-methyl-7,8-dihydro-1,6-naphthyridin-6(5H)-yl)methanone. LC-MS: 338.4 [M+H]⁺. ¹H NMR (500 MHz, DMSO-d₆) δ 8.39 (dd, J = 14.6, 4.4 Hz, 1H), 8.18 – 8.06 (m, 1H), 7.79 – 7.54 (m, 1H), 7.28 – 7.17 (m, 1H), 6.30 – 5.65 (m, 1H), 5.33 – 4.66 (m, 1H), 3.88 (s, 3H), 3.61 – 3.51 (m, 1H), 3.20 – 3.12 (m, 1H), 3.03 – 2.86 (m, 2H), 2.43 – 2.34 (m, 3H), 1.66 – 1.51 (m, 3H).

Example 161: (R)-6-(7-Chloro-1H-benzo[d]imidazole-2-carbonyl)-5-methyl-5,6,7,8-tetrahydro-1,6-naphthyridine-2-carbonitrile



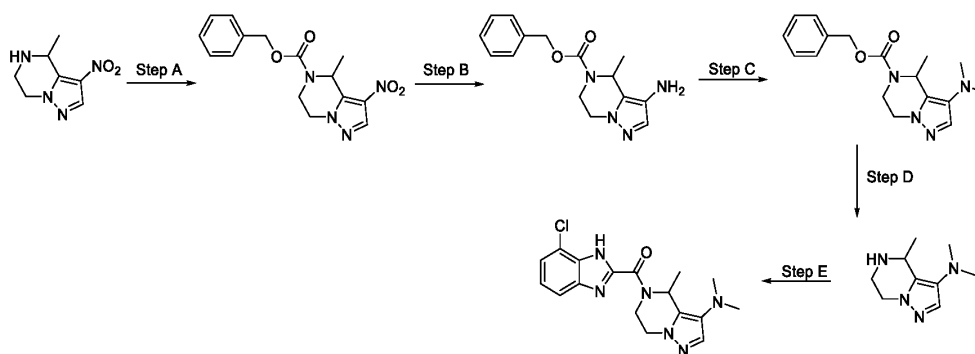
[00613] Step A: (R)-6-(tert-Butoxycarbonyl)-5-methyl-5,6,7,8-tetrahydro-1,6-naphthyridine 1-oxide (48.0 mg, 0.182 mmol), prepared as in Example 119, steps A and B, was dissolved in DCM (1.00 mL) under nitrogen. The solution was stirred when trimethylsilyl cyanide (40.1 μ L, 0.314 mmol) was added dropwise. After several minutes of additional stirring, dimethylcarbamy chloride (30.0 μ L, 0.320 mmol) was added dropwise. The mixture was stirred for 48 h. Saturated aqueous NaHCO_3 (30 mL) was added, and the mixture was extracted with DCM (3 x 10 mL). The combined organic layers were washed with water (10 mL), and brine (2 x 10 mL), dried over anhydrous MgSO_4 , filtered and concentrated to give tert-butyl (R)-2-cyano-5-methyl-7,8-dihydro-1,6-naphthyridine-6(5H)-carboxylate, which was used without further purification. LC-MS: 274.2 $[\text{M}+\text{H}]^+$.

[00614] Step B: tert-Butyl (R)-2-cyano-5-methyl-7,8-dihydro-1,6-naphthyridine-6(5H)-carboxylate (51.9 mg, 190.0 μ mol) was treated with TFA (5% in HFIP) (1.77 mL, 1.33 mmol) at room temperature for 2 h. iPrOH was added and the mixture was concentrated. The residue was co-evaporated with iPrOH twice more and dried overnight to give (R)-2-cyano-5-methyl-5,6,7,8-tetrahydro-1,6-naphthyridin-6-ium 2,2,2-trifluoroacetate. The resulting crude material was used without further purification. LC-MS: 174.1 $[\text{M}+\text{H}]^+$.

[00615] Step C: (R)-2-Cyano-5-methyl-5,6,7,8-tetrahydro-1,6-naphthyridin-6-ium 2,2,2-trifluoroacetate (59.4 mg, 0.207 mmol) was taken in MeCN (2.08 mL) and basified with saturated aqueous NaHCO_3 (3.00 mL, 1.03 mmol). Then, 7-chloro-2-(trichloromethyl)-1H-benzo[d]imidazole (55.8 mg, 0.207 mmol) was added in one portion. After 30 min of additional stirring, the mixture was diluted with more saturated aqueous NaHCO_3 (30 mL) and extracted with EtOAc (3 x 10 mL). The combined organic layers were washed with water (10 mL), and brine (2 x 10 mL), dried over anhydrous Na_2SO_4 , filtered and concentrated. This material was taken in DMSO (10% water) and filtrated on a 0.45 μ m PTFE filter. The filtrate was purified by semi-prep HPLC-MS (Column: CSH Prep C18 OBD, 5 μ m, 30 x 75 mm. Gradient: isocratic at 35% B for 1 min, 35% to 55% B in 8 min, 55% to 100% B in 0.1 min, hold 100% B for 2.9 min. Eluents: A = Milli Q H_2O + 10 mM ammonium bicarbonate pH = 10; B = MeCN. Solvent at 40 $^\circ\text{C}$. Flow: 45 mL/min. Run Time: 12 min). The tubes with the desired product were combined, concentrated, and lyophilized to give (R)-6-(7-chloro-1H-benzo[d]imidazole-2-

carbonyl)-5-methyl-5,6,7,8-tetrahydro-1,6-naphthyridine-2-carbonitrile. LC-MS: 350.5 / 352.4 [M+H]⁺. ¹H NMR (500 MHz, DMSO-d₆) δ 13.53 (br s, 1H), 8.12 – 7.85 (m, 2H), 7.54 (br s, 1H), 7.40 – 7.27 (m, 2H), 5.91 – 5.60 (m, 1H), 4.80 – 3.39 (m, 1H), 3.27 – 2.82 (m, 3H), 1.76 – 1.55 (m, 3H). Mixture of rotamers.

Example 162: (7-Chloro-1H-benzo[d]imidazol-2-yl)(3-(dimethylamino)-4-methyl-6,7-dihydropyrazolo[1,5-a]pyrazin-5(4H)-yl)methanone



[00616] Step A: 4-methyl-3-nitro-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrazine (300 mg, 1.65 mmol) was taken in THF (2.60 mL) and aqueous saturated NaHCO₃ (701 uL) at room temperature. the mixture was stirred at 0 °C when benzyl chloroformate (301 uL, 2.03 mmol) was added dropwise. The mixture warmed to room temperature and stirred overnight. The reaction was diluted with aqueous saturated NaHCO₃. The aqueous layer was extracted with EtOAc. The combined organic layers were washed with brine, dried over anhydrous Na₂SO₄, filtered, and concentrated under reduced pressure. The crude material was purified by flash chromatography on silica gel using a solution of EtOAc in heptanes (0 to 100% gradient) to give benzyl 4-methyl-3-nitro-6,7-dihydropyrazolo[1,5-a]pyrazine-5(4H)-carboxylate. LC-MS: 317.2 [M+H]⁺. ¹H NMR (400 MHz, CDCl₃) δ 8.11 (s, 1H), 7.42 – 7.32 (m, 5H), 6.02 – 5.80 (m, 1H), 5.30 – 5.16 (m, 2H), 4.67 – 4.43 (m, 1H), 4.32 – 4.04 (m, 2H), 3.64 – 3.42 (m, 1H), 1.57 (d, J = 6.5 Hz, 3H).

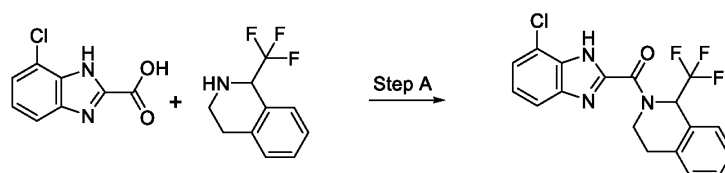
[00617] Step B: Benzyl 4-methyl-3-nitro-6,7-dihydropyrazolo[1,5-a]pyrazine-5(4H)-carboxylate (386 mg, 1.22 mmol) was taken in EtOH (10.0 mL) and water (2.50 mL) at room temperature. NH₄Cl (279 mg, 5.21 mmol) and Iron (675 mg, 12.1 mmol) were added, the flask was equipped with a water condenser, and the mixture was stirred at reflux for 1 h. The mixture was diluted with MeOH and filtered on celite. The filtrate was concentrated. The crude material was purified by flash chromatography on silica gel using a solution of MeOH and EtOAc (2:8) in EtOAc (0 to 50% gradient) to give benzyl 3-amino-4-methyl-6,7-dihydropyrazolo[1,5-a]pyrazine-5(4H)-carboxylate. LC-MS: 287.3 [M+H]⁺.

[00618] Step C: Benzyl 3-amino-4-methyl-6,7-dihydropyrazolo[1,5-a]pyrazine-5(4H)-carboxylate (44.0 mg, 0.154 mmol) was dissolved at room temperature in MeOH (800 uL) and AcOH (150 uL, 2.63 mmol). The solution was stirred when formaldehyde (36% in water, 60.0 uL, 0.784 mmol) was added. After a few additional minutes of stirring, NaBH₃CN (46.0 mg, 0.718 mmol) was added. Stirring was continued for 1 h. The reaction mixture was purified directly by reverse chromatography on a C-18 column using a solution of MeCN in 10 mM of ammonium bicarbonate in water pH = 10 (5 to 90% gradient). The tubes with the desired product were combined, concentrated, and lyophilized to give benzyl 3-(dimethylamino)-4-methyl-6,7-dihydropyrazolo[1,5-a]pyrazine-5(4H)-carboxylate. LC-MS: 315.3 [M+H]⁺.

[00619] Step D: Benzyl 3-(dimethylamino)-4-methyl-6,7-dihydropyrazolo[1,5-a]pyrazine-5(4H)-carboxylate (35.7 mg, 0.114 mmol) was dissolved in 2,2,2-trifluoroethanol (1.00 mL) at room temperature. The solution was stirred vigorously, evacuated, and refilled with nitrogen. Pd/C (10% wt, 6.04 mg, 0.00568 mmol) was added, the mixture was evacuated, and the atmosphere was refilled with nitrogen (repeated twice). The nitrogen balloon was replaced with one of hydrogen. The mixture was evacuated, and the atmosphere was refilled with hydrogen. The mixture was stirred under hydrogen overnight, evacuated and refilled with nitrogen. The mixture was filtered on a 0.45 µm PTFE filter and the filtrate was concentrated to give N,N,4-trimethyl-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrazin-3-amine. LC-MS: 181.1 [M+H]⁺.

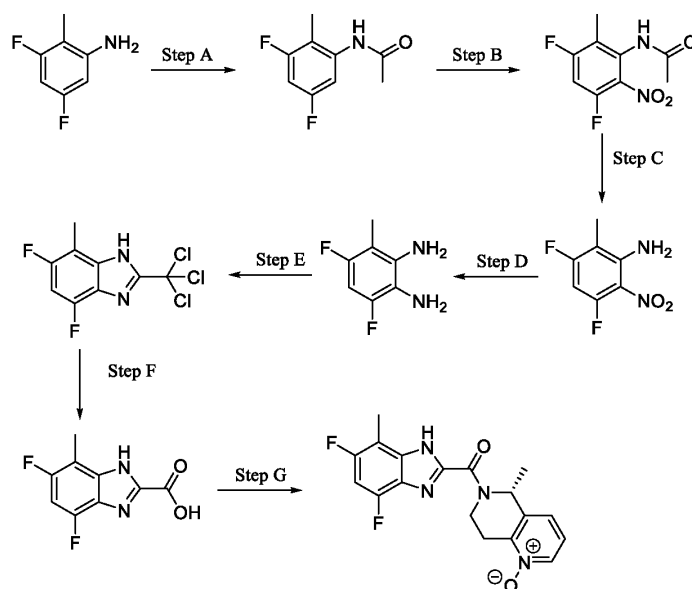
[00620] Step E: N,N,4-Trimethyl-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrazin-3-amine (20.5 mg, 0.114 mmol) and 7-chloro-1H-benzo[d]imidazole-2-carboxylic acid (26.9 mg, 0.137 mmol) were taken in DMF (1.00 mL) at room temperature. The mixture was stirred when DIPEA (60.0 uL, 0.341 mmol) and HATU (55.0 mg, 0.145 mmol) were added. After 1 h of additional stirring, aqueous NaOH (5 M) (200 uL, 1.00 mmol) was added and the mixture was allowed to stir overnight. The reaction mixture was purified by reverse chromatography on a C-18 column using a solution of MeCN/MeOH (1:1) in 10 mM of ammonium bicarbonate in water pH = 10 (5 to 90% gradient). The tubes with the desired product were combined, concentrated, and lyophilized to give (7-chloro-1H-benzo[d]imidazol-2-yl)(3-(dimethylamino)-4-methyl-6,7-dihydropyrazolo[1,5-a]pyrazin-5(4H)-yl)methanone. LC-MS: 359.5/361.4 [M+H]⁺. ¹H NMR (400 MHz, DMSO-d₆) δ 13.63 – 13.52 (m, 1H), 7.57 – 7.47 (m, 1H), 7.43 – 7.22 (m, 3H), 6.03 – 5.77 (m, 1H), 4.83 (dd, J = 14.3, 4.6 Hz, 0.5H), 4.31 – 4.20 (m, 1H), 4.15 (td, J = 12.2, 3.9 Hz, 0.5H), 4.02 (td, J = 12.1, 4.3 Hz, 0.5H), 3.95 – 3.82 (m, 0.5H), 3.68 – 3.54 (m, 1H), 2.70 – 2.57 (m, 6H), 1.60 – 1.48 (m, 3H). A mixture of rotamers.

Example 163: (7-Chloro-1H-benzo[d]imidazol-2-yl)(1-(trifluoromethyl)-3,4-dihydroisoquinolin-2(1H)-yl)methanone



[00621] Step A: (7-Chloro-1H-benzo[d]imidazol-2-yl)(1-(trifluoromethyl)-3,4-dihydroisoquinolin-2(1H)-yl)methanone was prepared from 1-(trifluoromethyl)-1,2,3,4-tetrahydroisoquinoline according to the procedure of Example 1, Step A. LC-MS: 380.2 [M+H]⁺. ¹H NMR (400 MHz, CDCl₃) δ 13.69 (s, 1H), 7.55 (d, J = 7.6 Hz, 2H), 7.43 – 7.23 (m, 5H), 6.46 (q, J = 8.4 Hz, 0.5H), 5.59 (s, 0.5H), 4.75 (dt, J = 13.6, 4.9 Hz, 0.5H), 3.95 – 3.81 (m, 0.5H), 3.44 – 3.37 (m, 0.5H), 3.21 – 3.11 (m, 0.5H), 3.08 – 2.97 (m, 2H). Multiple rotamers present.

Example 164: (R)-(4,6-Difluoro-7-methyl-1H-benzo[d]imidazol-2-yl)(5-methyl-7,8-dihydro-1,6-naphthyridin-6(5H)-yl)methanone

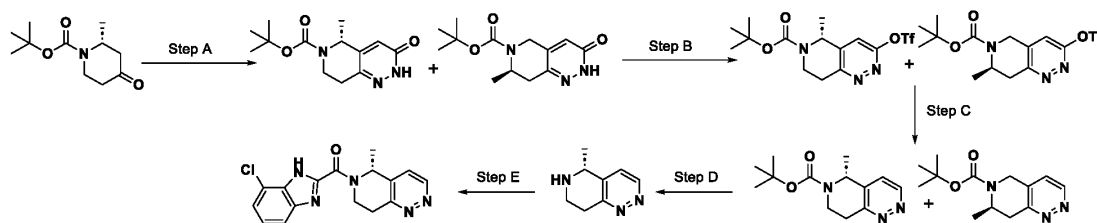


[00622] Steps A, B, C, D, E and F: 4,6-Difluoro-7-methyl-1H-benzo[d]imidazole-2-carboxylic acid was prepared from 3,5-difluoro-2-methylaniline according to Example 106, Steps A, B, C, D, E and F. LC-MS: [M+H]⁺ = 213.2 [M+H]⁺.

[00623] Step G: (R)-(4,6-Difluoro-7-methyl-1H-benzo[d]imidazol-2-yl)(5-methyl-7,8-dihydro-1,6-naphthyridin-6(5H)-yl)methanone was prepared from 4,6-difluoro-7-methyl-1H-benzo[d]imidazole-2-carboxylic acid and (R)-6-(tert-butoxycarbonyl)-5-methyl-5,6,7,8-tetrahydro-1,6-naphthyridine 1-oxide (Example 119), according to Example 1, Step A. LC-MS: 343.1 [M+H]⁺. ¹H NMR (400 MHz, DMSO-d₆) δ 14.01 – 13.40 (m, 1H), 8.83 – 8.53 (m, 1H),

8.47 – 7.99 (m, 1H), 7.84 – 7.51 (m, 1H), 7.29 – 7.05 (m, 1H), 6.58 – 5.76 (m, 1H), 5.61 – 4.53 (m, 1H), 3.74 – 3.67 (m, 1H), 3.22 – 3.14 (m, 2H), 2.45 – 2.41 (m, 3H), 1.79 – 1.55 (m, 3H).

Example 165: (R)-(7-Chloro-1H-benzo[d]imidazol-2-yl)(5-methyl-7,8-dihydropyrido[4,3-c]pyridazin-6(5H)-yl)methanone



[00624] Step A: A flask containing (R)-tert-butyl 2-methyl-4-oxopiperidine-1-carboxylate (2.00 g, 9.38 mmol), glyoxylic acid monohydrate (1.15 g, 12.2 mmol) and potassium acetate (46.5 mg, 0.469 mmol) in MeCN (10.0 mL) was heated at 90 °C for 12h, then cooled and stirred for 36h at 25 °C. Concentrated under reduced pressure and added, then re-heated the mixture to 90 °C and added hydrazine hydrate solution (1.59 mL, 28.1 mmol) in one portion, then stirred for an additional 16h at 110 °C. Concentrated under reduced pressure and purified directly by reverse phase flash column chromatography on C-18 (60 g, 0-100% MeCN/10mM AMF pH3.8, 0-1% MeOH). Concentrated pure fractions under reduced pressure and re-partitioned into MeTHF. Rinsed the organics with brine (1x) and dried (Na₂SO₄). Filtered and concentrated under reduced pressure to give a mixture of regioisomers (R)-tert-butyl 3-hydroxy-5-methyl-7,8-dihydropyrido[4,3-c]pyridazine-6(5H)-carboxylate and (R)-tert-butyl 3-hydroxy-7-methyl-7,8-dihydropyrido[4,3-c]pyridazine-6(5H)-carboxylate. LC-MS: 266.3 [M+H]⁺.

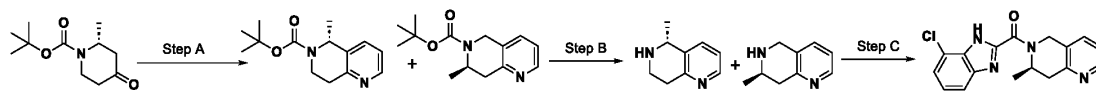
[00625] Step B: To a solution of (R)-tert-butyl 3-hydroxy-5-methyl-7,8-dihydropyrido[4,3-c]pyridazine-6(5H)-carboxylate (158 mg, 0.596 mmol) and (R)-tert-butyl 3-hydroxy-7-methyl-7,8-dihydropyrido[4,3-c]pyridazine-6(5H)-carboxylate (318 mg, 1.20 mmol) in THF (5.93 mL) was added sodium hydride (60% in dispersion in mineral oil, 31.0 mg, 0.774 mmol) and stirred for 15 minutes at 0 °C, then added N-Phenyl-bis(trifluoromethanesulfonyl)imide (279 mg, 0.774 mmol) and stirred for 15 minutes warming to 25 °C. Quenched by the addition of water, concentrated THF and re-partitioned into EtOAc. Rinsed the organics with brine (2x) and dried (Na₂SO₄). Filtered and concentrated under reduced pressure with SiO₂ and purified by flash column chromatography on SiO₂ (40 g, 0-100% EtOAc/heptanes, 0-3% DCM). Concentrated purest fractions under reduced pressure to give a mixture of regioisomers (R)-tert-butyl 5-methyl-3-(((trifluoromethyl)sulfonyl)oxy)-7,8-dihydropyrido[4,3-c]pyridazine-6(5H)-carboxylate and (R)-tert-butyl 7-methyl-3-(((trifluoromethyl)sulfonyl)oxy)-7,8-dihydropyrido[4,3-c]pyridazine-6(5H)-carboxylate. LC-MS: 398.3 [M+H]⁺.

[00626] Step C: To a solution of (R)-tert-butyl 5-methyl-3-(((trifluoromethyl)sulfonyl)oxy)-7,8-dihydropyrido[4,3-c]pyridazine-6(5H)-carboxylate (161 mg, 0.405 mmol) and (R)-tert-butyl 7-methyl-3-(((trifluoromethyl)sulfonyl)oxy)-7,8-dihydropyrido[4,3-c]pyridazine-6(5H)-carboxylate (322 mg, 0.810 mmol) in dioxane (4.02 mL) and water (402 μ L) was added 1,1'-bis(diphenylphosphino)ferrocene dichloropalladium (II) (15.1 mg, 0.0203 mmol), N,N-diisopropylethylamine (355 μ L, 2.03 mmol) and formic acid (156 μ L, 4.05 mmol) and sparged for 5 minutes with N₂, then heated at 110 °C for 16h. Cooled to 25 °C, concentrated dioxane under reduced pressure and re-partitioned between EtOAc and water. Rinsed the organics with brine (1x), filtered the organic layer through a PTFE filter (0.45 micron) and dried (Na₂SO₄). Filtered and concentrated under reduced pressure with SiO₂ and purified by flash column chromatography on SiO₂ (40 g, 0-20% iPrOH/DCM) to afford (R)-tert-butyl 5-methyl-7,8-dihydropyrido[4,3-c]pyridazine-6(5H)-carboxylate and (R)-tert-butyl 7-methyl-7,8-dihydropyrido[4,3-c]pyridazine-6(5H)-carboxylate. LC-MS: 250.3 [M+H]⁺.

[00627] Step D: To a solution of (R)-tert-butyl 5-methyl-7,8-dihydropyrido[4,3-c]pyridazine-6(5H)-carboxylate (53.7 mg, 0.215 mmol) in DCM (2.12 mL) was added trifluoroacetic acid (83.3 μ L, 1.08 mmol) and stirred for 30 minutes at 25 °C. Concentrated under reduced pressure and purified directly by reverse phase flash column chromatography on C-18 (30 g, 0-100% MeCN/H₂O). Lyophilized pure fractions to give (R)-5-methyl-5,6,7,8-tetrahydropyrido[4,3-c]pyridazine. LC-MS: 150.1 [M+H]⁺.

[00628] Step E: To a solution of (R)-5-methyl-5,6,7,8-tetrahydropyrido[4,3-c]pyridazine (32.1 mg, 0.215 mmol) in MeCN (2.12 mL) with aq. sat. sodium bicarbonate (1.96 mL, 2.15 mmol) at 0 °C was added solid 7-chloro-2-(trichloromethyl)-1H-benzo[d]imidazole (87.1 mg, 0.323 mmol) and stirred for 10 minutes warming to 25 °C. Concentrated MeCN under reduced pressure and sonicated to form a black suspension. Filtered and rinsed the cake with water, then purified the cake by prep-HPLC-MS (Column: CSH Prep C18 OBD, 5 μ m, 30 x 75 mm. Gradient: isocratic at 20% B for 1 min, 20% to 40% B in 8 min, 40% to 100% B in 0.1 min, hold 100% B for 2.9 min. Eluents: A = Milli Q H₂O + 10 mM AmF pH = 3.8; B = MeCN. Solvent at 40 °C. Flow: 45 mL/min. Run Time: 12 min). Lyophilized to give (R)-(7-chloro-1H-benzo[d]imidazol-2-yl)(5-methyl-7,8-dihydropyrido[4,3-c]pyridazin-6(5H)-yl)methanone. LC-MS: 328.4 [M+H]⁺. ¹H NMR (400 MHz, DMSO-d₆) δ 9.12 – 9.04 (m, 1H), 8.43 (br s, 1H), 7.73 – 7.60 (m, 1H), 7.57 – 7.53 (m, 1H), 7.38 – 7.27 (m, 2H), 6.48 – 6.39 (m, 0.4H), 5.80 (q, J = 6.7 Hz, 0.6H), 5.74 – 5.63 (m, 0.6H), 4.79 (dd, J = 13.7, 5.0 Hz, 0.4H), 3.79 – 3.69 (m, 1H), 3.24 – 3.17 (m, 2H), 1.74 (d, J = 6.8 Hz, 1H), 1.58 (d, J = 6.8 Hz, 2H).

Example 166: (R)-(7-Chloro-1H-benzo[d]imidazol-2-yl)(7-methyl-7,8-dihydro-1,6-naphthyridin-6(5H)-yl)methanone



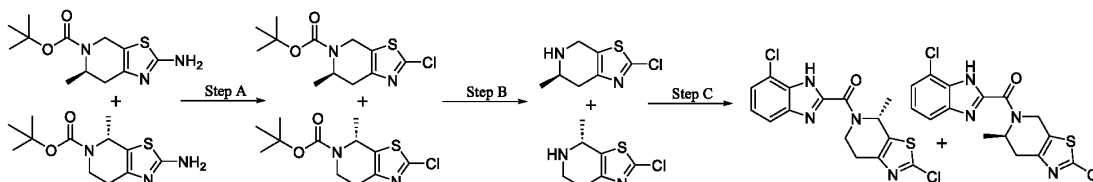
[00629] Step A: To a solution of (R)-tert-butyl 2-methyl-4-oxopiperidine-1-carboxylate (5.00 g, 23.4 mmol) and copper(II)chloride (325 mg, 2.34 mmol) in iPrOH (57.0 mL) was added propargylamine (2.30 mL, 35.2 mmol) and stirred for 2h at 60 °C. Cooled to room temperature and filtered through PTFE (0.45 micron), then concentrated the filtrate under reduced pressure and re-partitioned between EtOAc and water. Rinsed with aq. sat. NH₄Cl, brine and dried (Na₂SO₄). Filtered and concentrated under reduced pressure and the residue was purified by flash column chromatography (0-100% EtOAc/heptanes) to give a mixture of (R)-tert-butyl 7-methyl-7,8-dihydro-1,6-naphthyridine-6(5H)-carboxylate and (R)-tert-butyl 5-methyl-7,8-dihydro-1,6-naphthyridine-6(5H)-carboxylate. LC-MS: 249.2 [M+H]⁺.

[00630] Step B: To a solution containing (R)-tert-butyl 7-methyl-7,8-dihydro-1,6-naphthyridine-6(5H)-carboxylate (100 mg, 0.403 mmol) and (R)-tert-butyl 5-methyl-7,8-dihydro-1,6-naphthyridine-6(5H)-carboxylate (100 mg, 0.403 mmol) in DCM (4.00 mL) was added trifluoroacetic acid (311 uL, 4.03 mmol) and stirred for 72h at room temperature. Concentrated under reduced pressure to obtain a mixture of (R)-7-methyl-5,6,7,8-tetrahydro-1,6-naphthyridine and (R)-5-methyl-5,6,7,8-tetrahydro-1,6-naphthyridine. LC-MS: 149.2 [M+H]⁺.

[00631] Step C: To a solution of (R)-7-methyl-5,6,7,8-tetrahydro-1,6-naphthyridine (59.7 mg, 0.403 mmol) and (R)-5-methyl-5,6,7,8-tetrahydro-1,6-naphthyridine (59.7 mg, 0.403 mmol) in DMF (2.00 mL) with N,N-diisopropylethylamine (709 uL, 4.03 mmol) and HATU (322 mg, 0.846 mmol) was added solid 7-chloro-1H-benzo[d]imidazole-2-carboxylic acid (158 mg, 0.806 mmol) and stirred for 1h at room temperature. Added 5.0M Sodium Hydroxide (403 uL, 2.01 mmol) and stirred overnight at room temperature. Diluted with EtOAc and rinsed the organics with 10% aq. LiCl, brine and dried (Na₂SO₄). Filtered and concentrated under reduced pressure, then purified directly by prep-HPLC-MS (Column: CSH Prep C18 OBD, 5 µm, 30 x 75 mm. Gradient: isocratic at 20% B for 1 min, 20% to 40% B in 8 min, 40% to 100% B in 0.1 min, hold 100% B for 2.9 min. Eluents: A = Milli Q H₂O + 10 mM AmB pH = 10.0; B = MeCN. Solvent at 40 °C. Flow: 45 mL/min. Run Time: 12 min). Lyophilized pure fractions to obtain (R)-(7-chloro-1H-benzo[d]imidazol-2-yl)(7-methyl-7,8-dihydro-1,6-naphthyridin-6(5H)-yl)methanone. LC-MS: 327.1 [M+H]⁺. ¹H NMR (500 MHz, DMSO-d₆) δ 13.37 (br s, 1H), 8.46 – 8.38 (m, 1H), 7.74 (d, J = 7.8 Hz, 0.6H), 7.61 – 7.56 (m, 0.4H), 7.56 – 7.49 (m, 1H), 7.36 – 7.20 (m, 3H), 6.08 – 6.01 (m, 0.4H), 5.97 – 5.88 (m, 0.6H), 5.30 (d, J = 18.4 Hz, 0.6H), 5.20 – 5.13 (m, 0.4H),

4.82 (d, $J = 18.3$ Hz, 0.4H), 4.47 (d, $J = 18.2$ Hz, 0.6H), 3.26 – 3.20 (m, 1H), 2.89 – 2.80 (m, 1H), 1.22 (d, $J = 6.8$ Hz, 3H).

Examples 167A and 167B: (R)-(7-Chloro-1H-benzo[d]imidazol-2-yl)(2-chloro-6-methyl-6,7-dihydrothiazolo[5,4-c]pyridin-5(4H)-yl)methanone and (R)-(7-Chloro-1H-benzo[d]imidazol-2-yl)(2-chloro-4-methyl-6,7-dihydrothiazolo[5,4-c]pyridin-5(4H)-yl)methanone



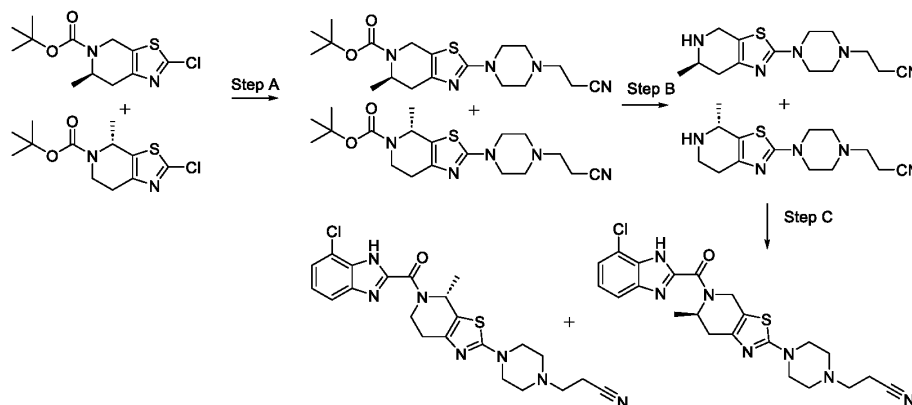
[00632] Step A: To a solution of (R)-tert-butyl 2-amino-6-methyl-6,7-dihydrothiazolo[5,4-c]pyridine-5(4H)-carboxylate (100 mg, 0.371 mmol) and (R)-tert-butyl 2-amino-4-methyl-6,7-dihydrothiazolo[5,4-c]pyridine-5(4H)-carboxylate (100 mg, 0.371 mmol), from Example 149, Step A, in MeCN (7.50 mL) with copper(II)chloride (124 mg, 0.891 mmol) was added isopentyl nitrite (124 μ L, 0.891 mmol) and stirred at 40 °C for 30 minutes. Cooled to 25 °C, concentrated MeCN and re-suspended in EtOAc. Filtered through a PTFE frit (0.45 micron) and the filtrate was rinsed with aq. sat. NH_4Cl (2x), brine (2x) and dried (Na_2SO_4). Filtered and concentrated under reduced pressure to gives a mixture of (R)-2-chloro-4-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridine 2,2,2-trifluoroacetate and (R)-2-chloro-6-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridine 2,2,2-trifluoroacetate. LC-MS: 233.2 $[\text{M}+\text{H}]^+$.

[00633] Step B: A 1:1 mixture of solution of (R)-2-chloro-4-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridine 2,2,2-trifluoroacetate and (R)-2-chloro-6-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridine 2,2,2-trifluoroacetate was prepared from a 1:1 mixture of (R)-tert-butyl 2-chloro-4-methyl-6,7-dihydrothiazolo[5,4-c]pyridine-5(4H)-carboxylate (33.0 mg, 0.114 mmol) and (R)-tert-butyl 2-chloro-6-methyl-6,7-dihydrothiazolo[5,4-c]pyridine-5(4H)-carboxylate (33.0 mg, 0.114 mmol) according to the procedure of Example 146, Step D. LC-MS: 189.1 $[\text{M}+\text{H}]^+$.

[00634] Step C: (R)-(7-Chloro-1H-benzo[d]imidazol-2-yl)(2-chloro-6-methyl-6,7-dihydrothiazolo[5,4-c]pyridin-5(4H)-yl)methanone (elutes first) and (R)-(7-chloro-1H-benzo[d]imidazol-2-yl)(2-chloro-4-methyl-6,7-dihydrothiazolo[5,4-c]pyridin-5(4H)-yl)methanone (elutes second) were prepared from a 1:1 mixture of (R)-2-chloro-4-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridine 2,2,2-trifluoroacetate and (R)-2-chloro-6-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridine 2,2,2-trifluoroacetate according the to the procedure of Example 148A and 148B, Step C. LC-MS: 367.3 $[\text{M}+\text{H}]^+$. Elutes first: ^1H NMR (500 MHz,

DMSO-d₆) δ 7.61 – 7.50 (m, 1H), 7.39 – 7.33 (m, 1H), 7.33 – 7.27 (m, 1H), 6.22 – 4.63 (m, 1H), 5.52 (d, J = 17.5 Hz, 0.5H), 4.30 (d, J = 17.5 Hz, 0.5H), 3.20 – 3.00 (m, 2H), 2.75 (d, J = 16.7 Hz, 1H), 1.31 – 1.25 (m, 3H). Elutes second: ¹H NMR (500 MHz, DMSO) δ 7.60 – 7.52 (m, 1H), 7.41 – 7.35 (m, 1H), 7.34 – 7.29 (m, 1H), 6.44 – 5.53 (m, 1H), 5.88 (q, J = 6.5 Hz, 0.7H), 4.73 (dd, J = 13.2, 4.7 Hz, 0.3H), 3.66 – 3.57 (m, 1H), 3.03 – 2.82 (m, 2H), 1.63 (dd, J = 90.0, 6.7 Hz, 3H). The regiochemistry for the first and second eluted compounds was arbitrarily assigned.

Examples 168A and 168B: (R)-3-(4-(5-(7-Chloro-1H-benzo[d]imidazole-2-carbonyl)-6-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)piperazin-1-yl)propanenitrile and (R)-3-(4-(5-(7-Chloro-1H-benzo[d]imidazole-2-carbonyl)-4-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)piperazin-1-yl)propanenitrile



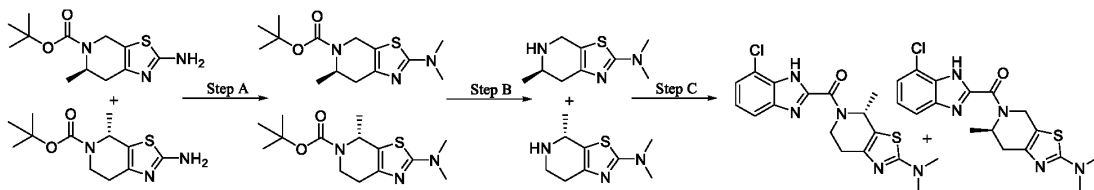
[00635] Step A: To a solution of a mixture of (R)-tert-butyl 2-chloro-4-methyl-6,7-dihydrothiazolo[5,4-c]pyridine-5(4H)-carboxylate (22.4 mg, 0.0776 mmol) and (R)-tert-butyl 2-chloro-6-methyl-6,7-dihydrothiazolo[5,4-c]pyridine-5(4H)-carboxylate (22.4 mg, 0.0776 mmol) (from Examples 167A and 167B), in DMSO (700 μ L) was added 1,4-diazabicyclo[2.2.2]octane (34.8 mg, 0.310 mmol) and potassium cyanide (11.6 mg, 0.171 mmol). The reaction mixture was stirred at 70 °C for 30 minutes, then 100 °C for 16h. Cooled to room temperature and diluted with EtOAc and aq. sat. NaHCO₃. Rinsed the organic layer with brine and dried (Na₂SO₄). Filtered and concentrated under reduced pressure to obtain a 1:1 mixture of (R)-tert-butyl 2-(4-(2-cyanoethyl)piperazin-1-yl)-4-methyl-6,7-dihydrothiazolo[5,4-c]pyridine-5(4H)-carboxylate and (R)-tert-butyl 2-(4-(2-cyanoethyl)piperazin-1-yl)-6-methyl-6,7-dihydrothiazolo[5,4-c]pyridine-5(4H)-carboxylate. LC-MS: 392.6 [M+H]⁺.

[00636] Step B: A 1:1 mixture of (R)-3-(4-(6-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)piperazin-1-yl)propanenitrile and (R)-3-(4-(4-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)piperazin-1-yl)propanenitrile was prepared from a 1:1 mixture of (R)-tert-butyl 2-

(4-(2-cyanoethyl)piperazin-1-yl)-4-methyl-6,7-dihydrothiazolo[5,4-c]pyridine-5(4H)-carboxylate and (R)-tert-butyl 2-(4-(2-cyanoethyl)piperazin-1-yl)-6-methyl-6,7-dihydrothiazolo[5,4-c]pyridine-5(4H)-carboxylate according to the procedure of Example 146, Step D. LC-MS: 263.3 [M+H]⁺.

[00637] Step C: To a solution of (R)-3-(4-(6-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)piperazin-1-yl)propanenitrile (16.4 mg, 0.0563 mmol) and (R)-3-(4-(4-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)piperazin-1-yl)propanenitrile (16.4 mg, 0.0563 mmol) in DMF (560 uL) with N,N-diisopropylethylamine (99.0 uL, 0.563 mmol) was added HATU (47.1 mg, 0.124 mmol) and stirred for 30 minutes at room temperature. Purified by prep-HPLC-MS (Column: CSH Prep C18 OBD, 5 μm, 30 x 75 mm. Gradient: isocratic at 30% B for 1 min, 30% to 50% B in 8 min, 50% to 100% B in 0.1 min, hold 100% B for 2.9 min. Eluents: A = Milli Q H₂O + 10 mM AmF pH = 3.8; B = MeCN. Solvent at 40 °C. Flow: 45 mL/min. Run Time: 12 min). Lyophilized each peak separately to provide (R)-3-(4-(5-(7-chloro-1H-benzo[d]imidazole-2-carbonyl)-6-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)piperazin-1-yl)propanenitrile (elutes first) and (R)-3-(4-(5-(7-chloro-1H-benzo[d]imidazole-2-carbonyl)-4-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-yl)piperazin-1-yl)propanenitrile (elutes second). LC-MS: 470.6 [M+H]⁺. Elutes first: ¹H NMR (400 MHz, DMSO-d₆) δ 13.44 (br s, 1H), 7.58 – 7.49 (m, 1H), 7.39 – 7.33 (m, 1H), 7.33 – 7.26 (m, 1H), 6.16 – 5.98 (m, 1H), 5.96 – 5.79 (m, 1H), 5.30 (d, J = 17.2 Hz, 1H), 5.26 – 5.21 (m, 0.4H), 4.53 (d, J = 16.3 Hz, 0.6H), 4.18 (d, J = 17.4 Hz, 1H), 3.33 – 3.32 (m, 2H), 3.03 – 2.84 (m, 2H), 2.73 – 2.68 (m, 2H), 2.65 – 2.60 (m, 2H), 2.56 – 2.51 (m, 4H), 1.28 (t, J = 6.6 Hz, 3H). Elutes second: ¹H NMR (400 MHz, DMSO-d₆) δ 13.47 (br s, 1H), 7.58 – 7.50 (m, 1H), 7.39 – 7.33 (m, 1H), 7.33 – 7.26 (m, 1H), 6.33 (br s, 0.5H), 5.65 (q, J = 6.3 Hz, 1H), 5.53 (br s, 1H), 4.73 – 4.64 (m, 0.5H), 3.60 – 3.50 (m, 1H), 3.37 – 3.36 (m, 2H), 2.83 – 2.73 (m, 1H), 2.73 – 2.66 (m, 2H), 2.66 – 2.58 (m, 3H), 2.57 – 2.51 (m, 5H), 1.62 (d, J = 6.5 Hz, 1H), 1.47 (d, J = 6.6 Hz, 2H). The regiochemistry for the first and second eluted compounds was assigned arbitrarily.

Examples 169A and 169B: (R)-(7-Chloro-1H-benzo[d]imidazol-2-yl)(2-(dimethylamino)-4-methyl-6,7-dihydrothiazolo[5,4-c]pyridin-5(4H)-yl)methanone and (R)-(7-Chloro-1H-benzo[d]imidazol-2-yl)(2-(dimethylamino)-6-methyl-6,7-dihydrothiazolo[5,4-c]pyridin-5(4H)-yl)methanone



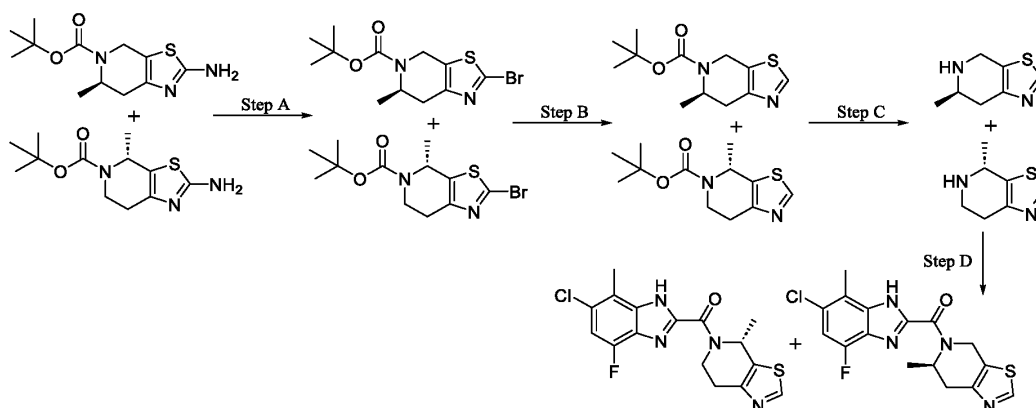
[00638] Step A: To a solution containing a 1:1 mixture of (R)-tert-butyl 2-amino-4-methyl-6,7-dihydrothiazolo[5,4-c]pyridine-5(4H)-carboxylate and (R)-tert-butyl 2-amino-6-methyl-6,7-dihydrothiazolo[5,4-c]pyridine-5(4H)-carboxylate (320 mg, 1.18 mmol) in THF (3.00 mL) with iodomethane (149 μ L, 2.38 mmol) at 0 °C was added sodium hydride (60% in dispersion in mineral oil, 119 mg, 2.97 mmol) and stirred for 1h. Increased temperature to 60 °C and stirred for 3h. Cooled to room temperature, concentrated under reduced pressure and re-partitioned between EtOAc and water. Basified to pH 8 with aq. sat. NaHCO₃, rinsed the organics with brine and dried (Na₂SO₄). Filtered and concentrated under reduced pressure to afford a 1:1 mixture of (R)-tert-butyl 2-(dimethylamino)-4-methyl-6,7-dihydrothiazolo[5,4-c]pyridine-5(4H)-carboxylate and (R)-tert-butyl 2-(dimethylamino)-6-methyl-6,7-dihydrothiazolo[5,4-c]pyridine-5(4H)-carboxylate. LC-MS: 298.4 [M+H]⁺.

[00639] Step B: A mixture of (R)-N,N,4-trimethyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-amine compound with (R)-N,N,6-trimethyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-amine was prepared from a mixture of (R)-tert-butyl 2-(dimethylamino)-4-methyl-6,7-dihydrothiazolo[5,4-c]pyridine-5(4H)-carboxylate and (R)-tert-butyl 2-(dimethylamino)-6-methyl-6,7-dihydrothiazolo[5,4-c]pyridine-5(4H)-carboxylate according to the procedure of Example 146, Step D. LC-MS: 198.2 [M+H]⁺.

[00640] Step C: (R)-(7-Chloro-1H-benzo[d]imidazol-2-yl)(2-(dimethylamino)-4-methyl-6,7-dihydrothiazolo[5,4-c]pyridin-5(4H)-yl)methanone (elutes first) and (R)-(7-chloro-1H-benzo[d]imidazol-2-yl)(2-(dimethylamino)-6-methyl-6,7-dihydrothiazolo[5,4-c]pyridin-5(4H)-yl)methanone (elutes second) were prepared from a mixture of (R)-tert-butyl 2-(dimethylamino)-4-methyl-6,7-dihydrothiazolo[5,4-c]pyridine-5(4H)-carboxylate and (R)-tert-butyl 2-(dimethylamino)-6-methyl-6,7-dihydrothiazolo[5,4-c]pyridine-5(4H)-carboxylate according to the procedure of Examples 168A and 168B, Step C. LC-MS: 376.5 [M+H]⁺. Elutes first: ¹H NMR (400 MHz, DMSO-d₆) δ 7.54 (d, J = 7.9 Hz, 1H), 7.36 (d, J = 7.6 Hz, 1H), 7.30 (t, J = 7.8 Hz, 1H), 6.31 – 6.20 (m, 0.35H), 5.63 (q, J = 6.5 Hz, 0.65H), 5.56 – 5.43 (m, 0.65H), 4.72 – 4.64 (m, 0.35H), 3.59 – 3.50 (m, 1H), 2.99 (d, J = 10.1 Hz, 6H), 2.82 – 2.66 (m, 1H), 2.62 (dd, J = 16.3, 3.2 Hz, 1H), 1.61 (d, J = 6.5 Hz, 1H), 1.47 (d, J = 6.6 Hz, 2H). Elutes second: ¹H NMR (400 MHz, DMSO-d₆) δ 7.54 (t, J = 7.2 Hz, 1H), 7.36 (d, J = 7.6 Hz, 1H), 7.30 (t, J = 7.8 Hz, 1H), 6.09 – 5.83 (m, 1H), 5.29 (d, J = 17.1 Hz, 1H), 4.53 (d, J = 17.0 Hz, 0.4H), 4.17 (d, J = 16.8 Hz, 0.6H), 2.99 (d, J = 9.1 Hz, 6H), 2.97 – 2.79 (m, 2H), 1.28 (t, J = 6.6 Hz, 3H). The regiochemistry for the first and second eluted compounds was assigned arbitrarily.

Examples 170A and 170B: (R)-(6-Chloro-4-fluoro-7-methyl-1H-benzo[d]imidazol-2-yl)(6-methyl-6,7-dihydrothiazolo[5,4-c]pyridin-5(4H)-yl)methanone and (R)-(6-Chloro-4-fluoro-

7-methyl-1H-benzo[d]imidazol-2-yl)(4-methyl-6,7-dihydrothiazolo[5,4-c]pyridin-5(4H-yl)methanone



[00641] Step A: A 1:1 mixture of (R)-tert-butyl 2-bromo-6-methyl-6,7-dihydrothiazolo[5,4-c]pyridine-5(4H)-carboxylate and (R)-tert-butyl 2-bromo-4-methyl-6,7-dihydrothiazolo[5,4-c]pyridine-5(4H)-carboxylate was prepared from a mixture of (R)-tert-butyl 2-amino-6-methyl-6,7-dihydrothiazolo[5,4-c]pyridine-5(4H)-carboxylate and (R)-tert-butyl 2-amino-4-methyl-6,7-dihydrothiazolo[5,4-c]pyridine-5(4H)-carboxylate (Example 149, Step A) according to the procedure of Example 146 Step B. LC-MS: 335.1 [M+H]⁺.

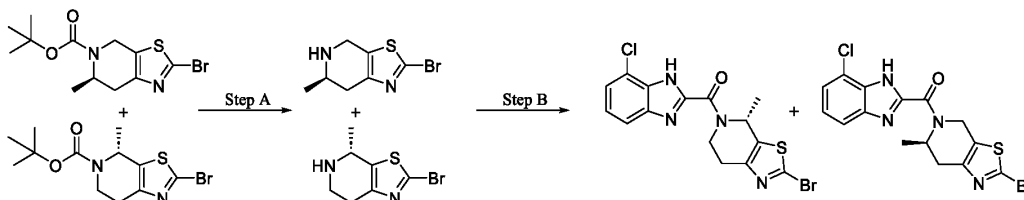
[00642] Step B: A mixture of tert-butyl (R)-6-methyl-6,7-dihydrothiazolo[5,4-c]pyridine-5(4H)-carboxylate and tert-butyl (R)-4-methyl-6,7-dihydrothiazolo[5,4-c]pyridine-5(4H)-carboxylate was prepared from a mixture of (R)-tert-butyl 2-bromo-6-methyl-6,7-dihydrothiazolo[5,4-c]pyridine-5(4H)-carboxylate and (R)-tert-butyl 2-bromo-4-methyl-6,7-dihydrothiazolo[5,4-c]pyridine-5(4H)-carboxylate according to the procedure of Examples of 148A and 148B, Step A. LC-MS: 255.4 [M+H]⁺.

[00643] Step C: A mixture of (R)-6-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridine and (R)-4-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridine was prepared from a mixture of tert-butyl (R)-6-methyl-6,7-dihydrothiazolo[5,4-c]pyridine-5(4H)-carboxylate and tert-butyl (R)-4-methyl-6,7-dihydrothiazolo[5,4-c]pyridine-5(4H)-carboxylate according to the procedure of Examples 148A and 148B, Step B. LC-MS: 155.2 [M+H]⁺.

[00644] Step D: (R)-(7-Chloro-1H-benzo[d]imidazol-2-yl)(2-(dimethylamino)-6-methyl-6,7-dihydrothiazolo[5,4-c]pyridin-5(4H)-yl)methanone (elutes first) and (R)-(6-chloro-4-fluoro-7-methyl-1H-benzo[d]imidazol-2-yl)(4-methyl-6,7-dihydrothiazolo[5,4-c]pyridin-5(4H)-yl)methanone (elutes second) was prepared from a mixture of (R)-6-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridine and (R)-4-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridine, and 6-chloro-4-fluoro-7-methyl-1H-benzo[d]imidazole-2-carboxylic acid (Example 129)

according to the procedure of Examples 168A and 168B, Step C. LC-MS: 365.4 [M+H]⁺. Elutes first: ¹H NMR (500 MHz, DMSO-d₆) δ 9.06 – 8.99 (m, 1H), 7.14 (d, J = 8.5 Hz, 1H), 6.08 – 5.53 (m, 1H), 5.69 – 5.32 (m, 1H), 4.77 – 4.31 (m, 1H), 3.24 – 3.05 (m, 1H), 2.81 (t, J = 17.3 Hz, 1H), 2.52 (s, 3H), 1.27 – 1.22 (m, 3H). N-H not apparent by ¹H NMR. Elutes second: ¹H NMR (500 MHz, DMSO-d₆) δ 13.75 (br s, 1H), 9.06 – 8.97 (m, 1H), 7.27 (dd, J = 10.3, 6.1 Hz, 1H), 6.37 – 5.86 (m, 1H), 5.39 – 4.75 (m, 1H), 3.63 – 3.34 (m, 1H), 3.07 – 2.83 (m, 2H), 2.53 (d, J = 7.6 Hz, 3H), 1.73 – 1.54 (m, 3H). The regiochemistry for the first and second eluted compounds was assigned arbitrarily.

Examples 171A and 171B: (R)-(2-Bromo-4-methyl-6,7-dihydrothiazolo[5,4-c]pyridin-5(4H)-yl)(7-chloro-1H-benzo[d]imidazol-2-yl)methanone and (R)-(2-Bromo-6-methyl-6,7-dihydrothiazolo[5,4-c]pyridin-5(4H)-yl)(7-chloro-1H-benzo[d]imidazol-2-yl)methanone

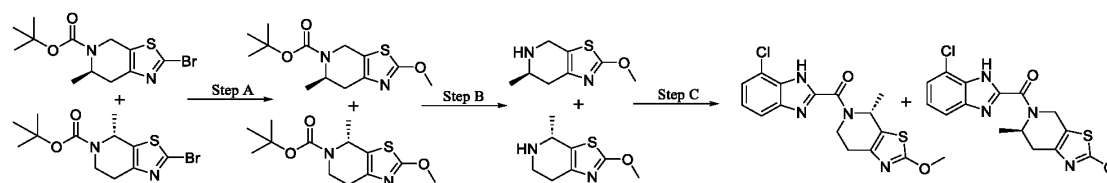


[00645] Step A: A mixture of (R)-2-bromo-6-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridine 2,2,2-trifluoroacetate and (R)-2-bromo-4-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridine 2,2,2-trifluoroacetate was prepared from a mixture of (R)-tert-butyl 2-bromo-6-methyl-6,7-dihydrothiazolo[5,4-c]pyridine-5(4H)-carboxylate (R)-tert-butyl 2-bromo-4-methyl-6,7-dihydrothiazolo[5,4-c]pyridine-5(4H)-carboxylate according to the procedure of Example 146, step D. LC-MS: 235.1 [M+H]⁺.

[00646] Step B: (R)-(2-Bromo-4-methyl-6,7-dihydrothiazolo[5,4-c]pyridin-5(4H)-yl)(7-chloro-1H-benzo[d]imidazol-2-yl)methanone (elutes second) and (R)-(2-bromo-6-methyl-6,7-dihydrothiazolo[5,4-c]pyridin-5(4H)-yl)(7-chloro-1H-benzo[d]imidazol-2-yl)methanone (elutes first) were prepared from a mixture of (R)-2-bromo-6-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridine 2,2,2-trifluoroacetate and (R)-2-bromo-4-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridine 2,2,2-trifluoroacetate according to the procedure of Examples 168A and 168B, Step C. LC-MS: 413.2 [M+H]⁺. Elutes first: ¹H NMR (500 MHz, DMSO-d₆) δ 7.60 – 7.50 (m, 1H), 7.38 – 7.34 (m, 1H), 7.34 – 7.28 (m, 1H), 6.26 – 5.45 (m, 1H), 6.09 – 5.24 (m, 1H), 4.71 – 4.25 (m, 1H), 3.22 – 3.02 (m, 1H), 2.78 (d, J = 16.4 Hz, 1H), 1.31 – 1.25 (m, 3H). NH proton not apparent. Elutes second: ¹H NMR (500 MHz, DMSO-d₆) δ 7.58 – 7.52 (m, 1H), 7.39 – 7.35 (m, 1H), 7.33 – 7.28 (m, 1H), 6.46 – 5.83 (m, 1H), 5.71 – 4.64 (m, 1H), 3.64 – 3.56 (m, 1H), 3.04 –

2.96 (m, 1H), 2.93 – 2.81 (m, 1H), 1.75 – 1.48 (m, 3H). NH proton not apparent. The regiochemistry for the first and second eluted compounds was assigned arbitrarily.

Examples 172A and 172B: (R)-(7-Chloro-1H-benzo[d]imidazol-2-yl)(2-methoxy-6-methyl-6,7-dihydrothiazolo[5,4-c]pyridin-5(4H)-yl)methanone and (R)-(7-Chloro-1H-benzo[d]imidazol-2-yl)(2-methoxy-4-methyl-6,7-dihydrothiazolo[5,4-c]pyridin-5(4H)-yl)methanone



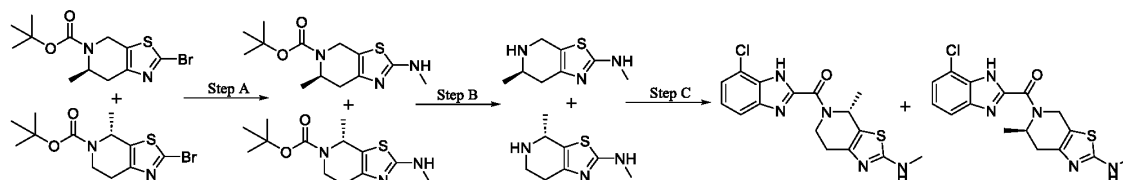
[00647] Step A: A flame-dried tube equipped with a stir bar and sealed with a screw cap was charged with (R)-tert-butyl 2-bromo-6-methyl-6,7-dihydrothiazolo[5,4-c]pyridine-5(4H)-carboxylate (45.0 mg, 0.135 mmol) and (R)-tert-butyl 2-bromo-4-methyl-6,7-dihydrothiazolo[5,4-c]pyridine-5(4H)-carboxylate (15.0 mg, 0.0450 mmol), tBuBrettPhos Pd G3 (15.7 mg, 0.0180 mmol), and sodium tert-butoxide (35.7 mg, 0.360 mmol). The reaction tube sealed was evacuated and backfilled with argon. Methanol (73.7 uL, 1.80 mmol) followed by dioxane (720 uL) were added via syringe. The reaction mixture was sonicated until there were no visible solids. The reaction was stirred at 60 °C for 48 h. The reaction was allowed to cool to room temperature before addition of EtOAc, and was then filtered through a pad of Celite and rinsed with EtOAc. The crude material was concentrated in vacuo afford the crude 1:1 mixture of tert-butyl (R)-2-methoxy-6-methyl-6,7-dihydrothiazolo[5,4-c]pyridine-5(4H)-carboxylate and tert-butyl (R)-2-methoxy-4-methyl-6,7-dihydrothiazolo[5,4-c]pyridine-5(4H)-carboxylate. LC-MS: 285.3 [M+H]⁺.

[00648] Step B: A mixture of (R)-2-methoxy-6-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridine 2,2,2-trifluoroacetate and (R)-4-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridine 2,2,2-trifluoroacetate was prepared from a mixture of tert-butyl (R)-2-methoxy-6-methyl-6,7-dihydrothiazolo[5,4-c]pyridine-5(4H)-carboxylate and tert-butyl (R)-2-methoxy-4-methyl-6,7-dihydrothiazolo[5,4-c]pyridine-5(4H)-carboxylate according to the procedure of Example 146, step D. LC-MS: 185.3 [M+H]⁺.

[00649] Step C: (R)-(7-Chloro-1H-benzo[d]imidazol-2-yl)(2-methoxy-6-methyl-6,7-dihydrothiazolo[5,4-c]pyridin-5(4H)-yl)methanone (elutes first) and (R)-(7-chloro-1H-benzo[d]imidazol-2-yl)(2-methoxy-4-methyl-6,7-dihydrothiazolo[5,4-c]pyridin-5(4H)-yl)methanone (elutes second) were prepared from a 1:1 mixture of tert-butyl (R)-2-methoxy-6-methyl-6,7-dihydrothiazolo[5,4-c]pyridine-5(4H)-carboxylate and tert-butyl (R)-2-methoxy-4-

methyl-6,7-dihydrothiazolo[5,4-c]pyridine-5(4H)-carboxylate according to the procedure of Example 165, step E. LC-MS: 362.5 [M+H]⁺. Elutes first: ¹H NMR (500 MHz, DMSO-d₆) δ 7.59 – 7.50 (m, 1H), 7.38 – 7.32 (m, 1H), 7.32 – 7.25 (m, 1H), 6.08 – 5.30 (m, 1H), 5.96 – 5.21 (m, 1H), 4.59 – 4.16 (m, 1H), 4.02 – 3.96 (m, 3H), 3.09 – 2.88 (m, 1H), 2.60 – 2.53 (m, 1H), 1.30 (t, J = 7.6 Hz, 3H). NH proton not apparent. Elutes second: ¹H NMR (500 MHz, DMSO-d₆) δ 7.58 – 7.51 (m, 1H), 7.37 – 7.31 (m, 1H), 7.31 – 7.25 (m, 1H), 6.28 – 5.61 (m, 1H), 5.60 – 4.68 (m, 1H), 4.01 – 3.97 (m, 3H), 3.61 – 3.55 (m, 1H), 2.89 – 2.79 (m, 1H), 2.71 – 2.64 (m, 1H), 1.67 – 1.47 (m, 3H). NH proton not apparent. The regiochemistry for the first and second eluted compounds was assigned arbitrarily.

Examples 173A and 173B: (R)-(7-Chloro-1H-benzo[d]imidazol-2-yl)(4-methyl-2-(methylamino)-6,7-dihydrothiazolo[5,4-c]pyridin-5(4H)-yl)methanone and (R)-(7-Chloro-1H-benzo[d]imidazol-2-yl)(6-methyl-2-(methylamino)-6,7-dihydrothiazolo[5,4-c]pyridin-5(4H)-yl)methanone



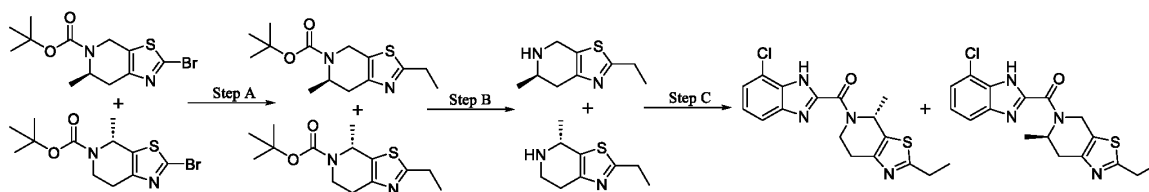
[00650] Step A: A flame-dried tube which was equipped with a magnetic stir bar was charged with the tBuBrettPhos Pd G3 (28.9 mg, 0.0331 mmol), tBuBrettPhos (16.4 mg, 0.0331 mmol), sodium tert-butoxide (65.6 mg, 0.662 mmol), and a mixture of (R)-tert-butyl 2-bromo-6-methyl-6,7-dihydrothiazolo[5,4-c]pyridine-5(4H)-carboxylate and (R)-tert-butyl 2-bromo-4-methyl-6,7-dihydrothiazolo[5,4-c]pyridine-5(4H)-carboxylate (60 mg, 0.18 mmol). The vessel was evacuated and backfilled with argon (this process was repeated a total of three times) and then a premixed solution of methylamine solution (2M in THF, 1.65 mL, 3.31 mmol), and tBuOH (1.32 mL) were added. The vial was sealed heated to 75 °C for 2 h. The reaction mixture was then diluted with ethyl acetate, filtered over a pad of Celite, and concentrated to afford a crude mixture of tert-butyl (R)-6-methyl-2-(methylamino)-6,7-dihydrothiazolo[5,4-c]pyridine-5(4H)-carboxylate and tert-butyl (R)-4-methyl-2-(methylamino)-6,7-dihydrothiazolo[5,4-c]pyridine-5(4H)-carboxylate. LC-MS: 284.4 [M+H]⁺.

[00651] Step B: A mixture of (R)-N,6-dimethyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-amine 2,2,2-trifluoroacetate and (R)-N,4-dimethyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-amine 2,2,2-trifluoroacetate was prepared from a mixture of tert-butyl (R)-6-methyl-2-(methylamino)-6,7-dihydrothiazolo[5,4-c]pyridine-5(4H)-carboxylate and tert-butyl (R)-4-

methyl-2-(methylamino)-6,7-dihydrothiazolo[5,4-c]pyridine-5(4H)-carboxylate according to the procedure of Example 146, step D. LC-MS: 184.2 [M+H]⁺.

[00652] Step C: (R)-(7-Chloro-1H-benzo[d]imidazol-2-yl)(6-methyl-2-(methylamino)-6,7-dihydrothiazolo[5,4-c]pyridin-5(4H)-yl)methanone (elutes first) and (R)-(7-chloro-1H-benzo[d]imidazol-2-yl)(4-methyl-2-(methylamino)-6,7-dihydrothiazolo[5,4-c]pyridin-5(4H)-yl)methanone (elutes second) were prepared from a mixture of (R)-N,6-dimethyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-amine 2,2,2-trifluoroacetate and (R)-N,4-dimethyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridin-2-amine 2,2,2-trifluoroacetate according to the procedure of Example 165, step E. LC-MS: 362.5 [M+H]⁺. Elutes first: ¹H NMR (500 MHz, DMSO-d₆) δ 7.58 – 7.51 (m, 1H), 7.46 – 7.38 (m, 1H), 7.37 – 7.33 (m, 1H), 7.32 – 7.27 (m, 1H), 5.97 – 5.76 (m, 1H), 5.30 – 5.18 (m, 1H), 4.53 – 4.09 (m, 1H), 2.97 – 2.81 (m, 1H), 2.82 – 2.76 (m, 3H), 2.48 – 2.44 (m, 1H), 1.31 – 1.25 (m, 3H). Elutes second: ¹H NMR (500 MHz, DMSO-d₆) δ 7.55 (d, J = 7.9 Hz, 1H), 7.45 – 7.38 (m, 1H), 7.38 – 7.35 (m, 1H), 7.32 – 7.28 (m, 1H), 6.22 – 5.54 (m, 1H), 5.54 – 4.62 (m, 1H), 3.58 – 3.51 (m, 1H), 3.32 – 3.25 (m, 1H), 2.78 (dd, J = 9.9, 4.7 Hz, 3H), 2.76 – 2.55 (m, 1H), 1.63 – 1.43 (m, 3H). NH proton not apparent. The regiochemistry for the first and second eluted compounds was assigned arbitrarily.

Example 174A and 174B: (R)-(7-Chloro-1H-benzo[d]imidazol-2-yl)(2-ethyl-4-methyl-6,7-dihydrothiazolo[5,4-c]pyridin-5(4H)-yl)methanone and (R)-(7-Chloro-1H-benzo[d]imidazol-2-yl)(2-ethyl-6-methyl-6,7-dihydrothiazolo[5,4-c]pyridin-5(4H)-yl)methanone



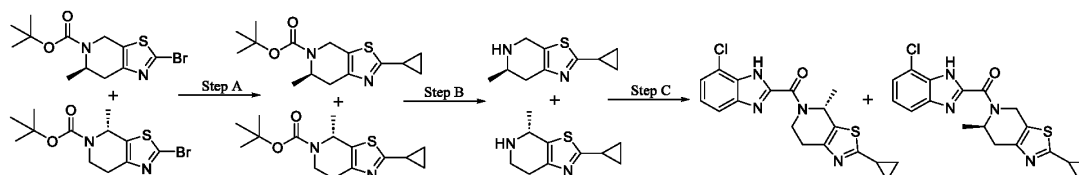
[00653] Step A: A solution of (R)-tert-butyl 2-bromo-6-methyl-6,7-dihydrothiazolo[5,4-c]pyridine-5(4H)-carboxylate (45.0 mg, 0.135 mmol) and (R)-tert-butyl 2-bromo-4-methyl-6,7-dihydrothiazolo[5,4-c]pyridine-5(4H)-carboxylate (15.0 mg, 0.0450 mmol), ethylboronic acid (26.6 mg, 0.360 mmol), bis(benzonitrile)dichloropalladium(II) (6.91 mg, 0.0180 mmol), 2-dicyclohexylphosphino-2',6'-dimethoxybiphenyl (11.4 mg, 0.0270 mmol), and potassium phosphate (tribasic, 117 mg, 0.540 mmol) in toluene (1.80 mL) was sparged with N₂ gas for 10 min. The reaction was sealed and allowed to stir at 100 °C for 2 h. The reaction was cooled to room temperature and diluted with EtOAc and water. The organic phase was separated and dried over anhydrous Na₂SO₄, filtered and concentrated to afford the crude mixture of regioisomers

tert-butyl (R)-2-ethyl-6-methyl-6,7-dihydrothiazolo[5,4-c]pyridine-5(4H)-carboxylate and tert-butyl (R)-2-ethyl-4-methyl-6,7-dihydrothiazolo[5,4-c]pyridine-5(4H)-carboxylate, which was used in the next step without further purification.

[00654] Step B: A mixture of (R)-2-ethyl-4-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridine trifluoroacetate and (R)-2-ethyl-6-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridine trifluoroacetate was prepared from a mixture of (R)-2-ethyl-6-methyl-6,7-dihydrothiazolo[5,4-c]pyridine-5(4H)-carboxylate and tert-butyl (R)-2-ethyl-4-methyl-6,7-dihydrothiazolo[5,4-c]pyridine-5(4H)-carboxylate according to the procedure of Example 146, step D. LC-MS: 183.2 [M+H]⁺.

[00655] Step C: (R)-(7-Chloro-1H-benzo[d]imidazol-2-yl)(2-ethyl-4-methyl-6,7-dihydrothiazolo[5,4-c]pyridin-5(4H)-yl)methanone (elutes first) and (R)-(7-chloro-1H-benzo[d]imidazol-2-yl)(2-ethyl-6-methyl-6,7-dihydrothiazolo[5,4-c]pyridin-5(4H)-yl)methanone (elutes second) was prepared from a mixture of (R)-2-ethyl-4-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridine trifluoroacetate and (R)-2-ethyl-6-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridine trifluoroacetate according to the procedure of Example 165, step E. LC-MS: 361.5 [M+H]⁺. Elutes first: ¹H NMR (500 MHz, DMSO-d₆) δ 7.57 – 7.51 (m, 1H), 7.37 – 7.31 (m, 1H), 7.31 – 7.25 (m, 1H), 6.32 – 5.44 (m, 1H), 6.02 – 5.26 (m, 1H), 4.73 – 4.27 (m, 1H), 3.19 – 3.00 (m, 1H), 2.99 – 2.90 (m, 2H), 2.74 (d, J = 16.3 Hz, 1H), 1.34 – 1.19 (m, 6H). Elutes second: ¹H NMR (500 MHz, DMSO-d₆) δ 7.56 – 7.52 (m, 1H), 7.38 – 7.31 (m, 1H), 7.30 – 7.25 (m, 1H), 6.51 – 6.36 (m, 1H), 5.82 (q, J = 6.4 Hz, 1H), 5.65 – 5.48 (m, 1H), 4.77 – 4.71 (m, 1H), 3.62 – 3.54 (m, 1H), 2.98 – 2.88 (m, 3H), 2.86 – 2.80 (m, 1H), 1.71 – 1.50 (m, 3H), 1.30 – 1.24 (m, 3H). NH proton not apparent. The regiochemistry for the first and second eluted compounds was assigned arbitrarily.

Example 175A and 175B: (R)-(7-Chloro-1H-benzo[d]imidazol-2-yl)(2-cyclopropyl-4-methyl-6,7-dihydrothiazolo[5,4-c]pyridin-5(4H)-yl)methanone and (R)-(7-Chloro-1H-benzo[d]imidazol-2-yl)(2-cyclopropyl-6-methyl-6,7-dihydrothiazolo[5,4-c]pyridin-5(4H)-yl)methanone



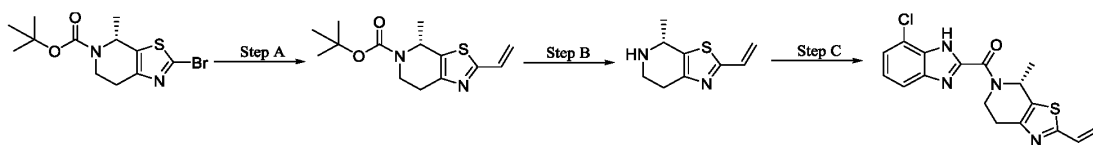
[00656] Step A: A mixture of tert-butyl (R)-2-cyclopropyl-4-methyl-6,7-dihydrothiazolo[5,4-c]pyridine-5(4H)-carboxylate and tert-butyl (R)-2-cyclopropyl-6-methyl-6,7-dihydrothiazolo[5,4-c]pyridine-5(4H)-carboxylate was prepared from a mixture of (R)-tert-butyl

2-bromo-6-methyl-6,7-dihydrothiazolo[5,4-c]pyridine-5(4H)-carboxylate and (R)-tert-butyl 2-bromo-4-methyl-6,7-dihydrothiazolo[5,4-c]pyridine-5(4H)-carboxylate and cyclopropylboronic acid according to the procedure of Examples 174A and 174B, Step A. LC-MS: 295.3 [M+H]⁺.

[00657] Step B: A mixture of (R)-2-cyclopropyl-4-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridine trifluoroacetate and (R)-2-cyclopropyl-6-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridine trifluoroacetate was prepared from a mixture of (R)-2-cyclopropyl-6-methyl-6,7-dihydrothiazolo[5,4-c]pyridine-5(4H)-carboxylate and tert-butyl (R)-2-cyclopropyl-4-methyl-6,7-dihydrothiazolo[5,4-c]pyridine-5(4H)-carboxylate according to the procedure of Example 146, step D. LC-MS: 195.2 [M+H]⁺.

[00658] Step C: (R)-(7-Chloro-1H-benzo[d]imidazol-2-yl)(2-cyclopropyl-4-methyl-6,7-dihydrothiazolo[5,4-c]pyridin-5(4H)-yl)methanone (elutes second) and (R)-(7-chloro-1H-benzo[d]imidazol-2-yl)(2-cyclopropyl-6-methyl-6,7-dihydrothiazolo[5,4-c]pyridin-5(4H)-yl)methanone (elutes first) was prepared from a mixture of (R)-2-cyclopropyl-4-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridine trifluoroacetate and (R)-2-cyclopropyl-6-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridine trifluoroacetate according to the procedure of Example 165, step E. LC-MS: 373.4 [M+H]⁺. Elutes first: ¹H NMR (500 MHz, DMSO-d₆) δ 7.59 – 7.51 (m, 1H), 7.39 – 7.33 (m, 1H), 7.33 – 7.27 (m, 1H), 6.30 – 5.42 (m, 1H), 6.00 – 5.24 (m, 1H), 4.72 – 4.24 (m, 1H), 3.13 – 2.96 (m, 1H), 2.69 (d, J = 16.4 Hz, 1H), 2.38 – 2.31 (m, 1H), 1.28 – 1.23 (m, 3H), 1.11 – 1.06 (m, 2H), 0.97 – 0.89 (m, 2H). NH proton not apparent. Elutes second: ¹H NMR (500 MHz, DMSO-d₆) δ 7.57 – 7.52 (m, 1H), 7.38 – 7.34 (m, 1H), 7.32 – 7.28 (m, 1H), 6.47 – 5.50 (m, 1H), 5.84 – 4.69 (m, 1H), 3.62 – 3.30 (m, 1H), 3.03 – 2.70 (m, 2H), 2.37 – 2.29 (m, 1H), 1.70 – 1.49 (m, 3H), 1.12 – 1.02 (m, 2H), 0.96 – 0.87 (m, 2H). NH proton not apparent. The regiochemistry for the first and second eluted compounds was assigned arbitrarily..

Example 176: (R)-(4-Chloro-1H-benzo[d]imidazol-2-yl)(4-methyl-2-vinyl-6,7-dihydrothiazolo[5,4-c]pyridin-5(4H)-yl)methanone



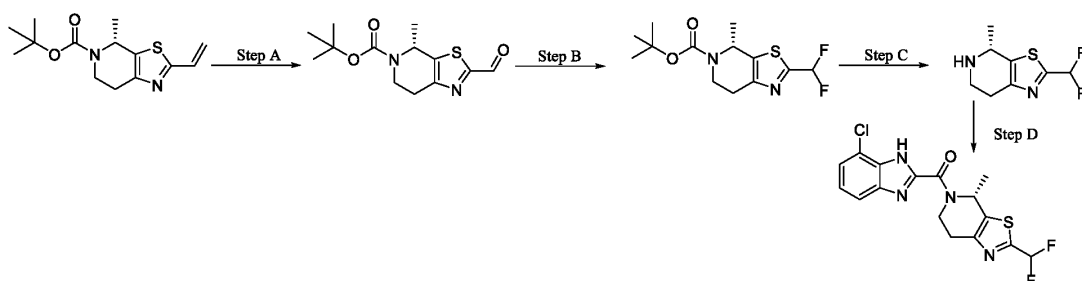
[00659] Step A: To a solution of tetrakis(triphenylphosphine)palladium(0) (37.2 mg, 0.0315 mmol) and copper(I) iodide (1.21 mg, 0.00630 mmol) in DMF (4.30 mL) was added a solution of (R)-tert-butyl 2-bromo-4-methyl-6,7-dihydrothiazolo[5,4-c]pyridine-5(4H)-carboxylate (210 mg, 0.630 mmol) in DMF (6.30 mL) and sparged with N₂ for 5 minutes, then added tributyl(vinyl)tin, 97% (228 uL, 0.756 mmol) and heated at 65 °C for 2h. Cooled to room temperature, diluted with EtOAc and 10% aq. KF and filtered the organic layer through a PTFE

filter (0.45 micron). Rinsed the organics with 10% aq. LiCl, brine and dried (Na₂SO₄). Filtered and concentrated under reduced pressure, then purified the residue by flash column chromatography (0-100% EtOAc/heptanes, 0-5% DCM). Concentrated under reduced pressure to obtain (R)-tert-butyl 4-methyl-2-vinyl-6,7-dihydrothiazolo[5,4-c]pyridine-5(4H)-carboxylate. LC-MS: 281.3 [M+H]⁺.

[00660] Step B: (R)-2-Vinyl-4-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridine trifluoroacetate was prepared from tert-butyl (R)-2-cyclopropyl-4-methyl-6,7-dihydrothiazolo[5,4-c]pyridine-5(4H)-carboxylate according to the procedure of Example 146, step D. LC-MS: 181.2 [M+H]⁺.

[00661] Step C: (R)-(4-Chloro-1H-benzo[d]imidazol-2-yl)(4-methyl-2-vinyl-6,7-dihydrothiazolo[5,4-c]pyridin-5(4H)-yl)methanone was prepared from (R)-2-vinyl-4-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridine trifluoroacetate according to the procedure of Examples 168A and 168B, Step C. LC-MS: 359.5 [M+H]⁺. ¹H NMR (400 MHz, DMSO-d₆) δ 13.54 (s, 1H), 7.75 (d, J = 7.9 Hz, 0.3H), 7.55 – 7.48 (m, 1H), 7.39 – 7.35 (m, 0.7H), 7.35 – 7.30 (m, 1H), 6.91 (dd, J = 17.5, 10.8 Hz, 1H), 6.62 (q, J = 6.7 Hz, 0.3H), 6.01 (dd, J = 17.5, 9.0 Hz, 1H), 5.88 (d, J = 5.0 Hz, 0.7H), 5.77 (dd, J = 13.7, 4.9 Hz, 0.7H), 5.57 (dd, J = 17.7, 10.8 Hz, 1H), 4.79 – 4.74 (m, 0.3H), 3.67 – 3.56 (m, 1H), 3.40 – 3.34 (m, 0.5H), 2.99 – 2.95 (m, 0.5H), 2.91 (dd, J = 16.0, 3.2 Hz, 1H), 1.73 (d, J = 6.6 Hz, 1H), 1.56 (d, J = 6.7 Hz, 2H).

Example 177: (R)-(7-Chloro-1H-benzo[d]imidazol-2-yl)(2-(difluoromethyl)-4-methyl-6,7-dihydrothiazolo[5,4-c]pyridin-5(4H)-yl)methanone



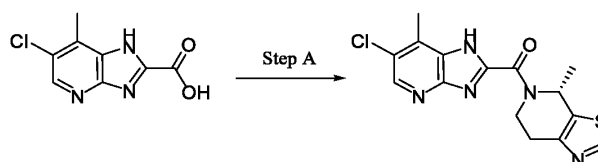
[00662] Step A: To a solution of (R)-tert-butyl 4-methyl-2-vinyl-6,7-dihydrothiazolo[5,4-c]pyridine-5(4H)-carboxylate (67.5 mg, 0.241 mmol) in acetone (270 uL) and water (75.0 uL) was added potassium osmate dihydrate (986 ug, 0.00267 mmol) followed by 4-methylmorpholine N-oxide (64.6 mg, 0.535 mmol) and stirred vigorously at room temperature for 16h. Added sodium periodate (116 mg, 0.535 mmol) and stirred for an additional 3h at room temperature, then diluted with EtOAc and 10% aq. Na₂S₂O₅. Rinsed the organics with brine and dried (Na₂SO₄). Filtered and concentrated under reduced pressure to obtain (R)-tert-butyl 2-formyl-4-methyl-6,7-dihydrothiazolo[5,4-c]pyridine-5(4H)-carboxylate. LC-MS: 283.1 [M+H]⁺.

[00663] Step B: To a solution of (R)-tert-butyl 2-formyl-4-methyl-6,7-dihydrothiazolo[5,4-c]pyridine-5(4H)-carboxylate (45.0 mg, 0.159 mmol) in DCM (1.70 mL) was added (diethylamino)sulfur trifluoride (87.6 μ L, 0.708 mmol) at 0 °C and stirred warming to room temperature for over 30 minutes. Heated at 40 °C for 30 minutes, then quenched by the addition of aq. sat. NaHCO₃ and stirred vigorously for 5 minutes, then extracted with DCM. Rinsed the combined organics with brine and dried (Na₂SO₄). Filtered and concentrated under reduced pressure to afford material which was used without purification in the next step. LC-MS: 249.2 [M-tBu+H]⁺.

[00664] Step C: (R)-2-(Difluoromethyl)-4-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridine was prepared from (R)-tert-butyl 2-(difluoromethyl)-4-methyl-6,7-dihydrothiazolo[5,4-c]pyridine-5(4H)-carboxylate according to the procedure of Example 146, step D. LC-MS: 205.2 [M+H]⁺.

[00665] Step D: (R)-(7-Chloro-1H-benzo[d]imidazol-2-yl)(2-(difluoromethyl)-4-methyl-6,7-dihydrothiazolo[5,4-c]pyridin-5(4H)-yl)methanone was prepared from (R)-2-(difluoromethyl)-4-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridine according to the procedure of Examples 168A and 168B, Step C. LC-MS: 383.3 [M+H]⁺. ¹H NMR (400 MHz, DMSO-d₆) δ 13.47 (br s, 1H), 7.58 – 7.52 (m, 0.8H), 7.49 – 7.43 (m, 0.3H), 7.39 – 7.34 (m, 0.7H), 7.35 – 7.29 (m, 1H), 7.20 – 7.16 (m, 0.2H), 6.50 (br s, 0.4H), 6.01 (q, J = 6.2 Hz, 0.6H), 5.69 (br s, 0.6H), 4.77 (dd, J = 13.0, 4.8 Hz, 0.4H), 3.67 – 3.58 (m, 1H), 3.11 – 3.02 (m, 1H), 2.98 (dd, J = 16.1, 3.5 Hz, 1H), 2.95 – 2.84 (m, 1H), 1.76 (d, J = 6.6 Hz, 1H), 1.59 (d, J = 6.7 Hz, 2H).

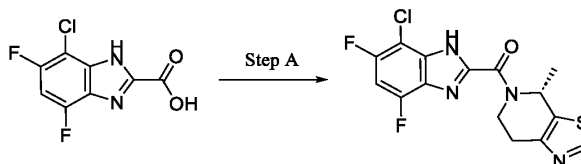
Example 178: (R)-(6-Chloro-7-methyl-1H-imidazo[4,5-b]pyridin-2-yl)(4-methyl-6,7-dihydrothiazolo[5,4-c]pyridin-5(4H)-yl)methanone



[00666] Step A: (R)-(6-Chloro-7-methyl-1H-imidazo[4,5-b]pyridin-2-yl)(4-methyl-6,7-dihydrothiazolo[5,4-c]pyridin-5(4H)-yl)methanone was prepared from 6-chloro-7-methyl-1H-imidazo[4,5-b]pyridine-2-carboxylic acid and a mixture of (R)-4-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridine 2,2,2-trifluoroacetate and (R)-6-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridine 2,2,2-trifluoroacetate (Examples 170A and 170B, Step B) according to the procedure of Examples 168A and 168B, Step C. LC-MS: 348.2 [M+H]⁺. ¹H NMR (400 MHz, CD₃CN) δ 8.81 – 8.72 (m, 1H), 8.43 (s, 1H), 6.93 – 6.84 (m, 1H), 6.00 – 5.86 (m, 1H), 4.93 – 4.81 (m, 0.5H), 3.64 – 3.51 (m, 0.5H), 3.37 – 3.29 (m, 0.5H), 3.16 – 3.03 (m,

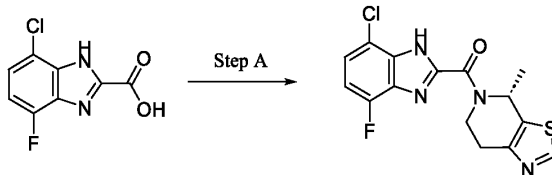
0.5H), 3.02 – 2.93 (m, 1.5H), 2.68 (s, 3H), 2.08 – 2.01 (m, 1H), 1.77 (d, J = 6.6 Hz, 1H), 1.59 (d, J = 6.7 Hz, 2H).

Example 179: (R)-(7-Chloro-4,6-difluoro-1H-benzo[d]imidazol-2-yl)(4-methyl-6,7-dihydrothiazolo[5,4-c]pyridin-5(4H)-yl)methanone



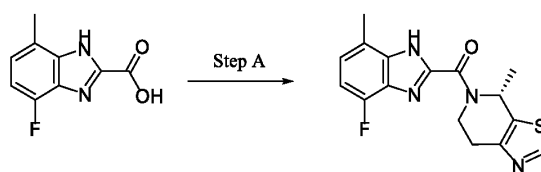
[00667] Step A: (R)-(7-Chloro-4,6-difluoro-1H-benzo[d]imidazol-2-yl)(4-methyl-6,7-dihydrothiazolo[5,4-c]pyridin-5(4H)-yl)methanone was prepared from 7-chloro-4,6-difluoro-1H-benzo[d]imidazole-2-carboxylic acid (Example 126, Step F) and a mixture of (R)-4-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridine 2,2,2-trifluoroacetate and (R)-6-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridine 2,2,2-trifluoroacetate (Examples 170A and 170B, Step B) according to the procedure of Examples 168A and 168B, Step C. LC-MS: 369.1 [M+H]⁺. ¹H NMR (400 MHz, CD₃CN) δ 8.77 (d, J = 8.1 Hz, 1H), 7.13 (t, J = 10.3 Hz, 1H), 6.77 – 5.83 (m, 1H), 5.83 – 4.71 (m, 1H), 3.65 – 3.28 (m, 1H), 3.14 – 2.89 (m, 2H), 1.77 – 1.55 (m, 3H).

Example 180: (R)-(4-Chloro-7-fluoro-1H-benzo[d]imidazol-2-yl)(4-methyl-6,7-dihydrothiazolo[5,4-c]pyridin-5(4H)-yl)methanone



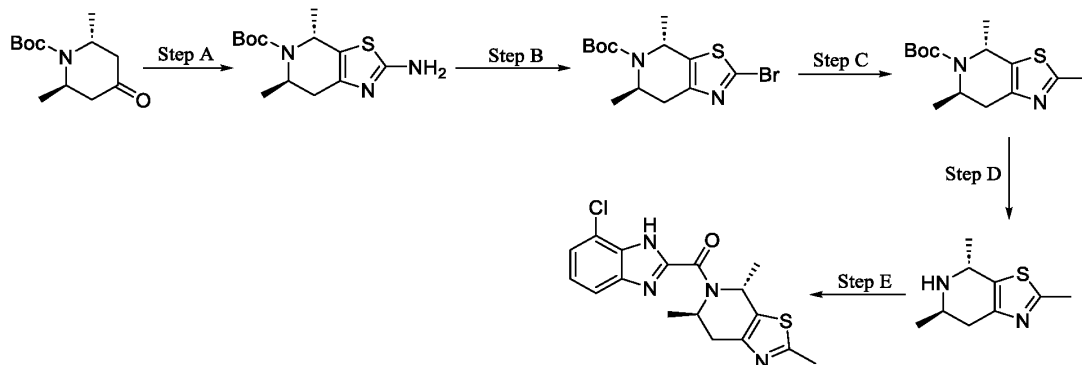
[00668] Step A: (R)-(4-Chloro-7-fluoro-1H-benzo[d]imidazol-2-yl)(4-methyl-6,7-dihydrothiazolo[5,4-c]pyridin-5(4H)-yl)methanone was prepared from 4-chloro-7-fluoro-1H-benzo[d]imidazole-2-carboxylic acid (Example 133, Step D) and a mixture of (R)-4-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridine 2,2,2-trifluoroacetate and (R)-6-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridine 2,2,2-trifluoroacetate (Examples 170A and 170B, Step B) according to the procedure of Examples 168A and 168B, Step C. LC-MS: 350.9 [M+H]⁺. ¹H NMR (500 MHz, DMSO-d₆) δ 14.09 (s, 1H), 9.10 – 8.97 (m, 1H), 7.46 – 7.31 (m, 1H), 7.27 – 7.08 (m, 1H), 6.31 – 5.84 (m, 1H), 5.35 – 4.70 (m, 1H), 3.70 – 3.33 (m, 1H), 3.12 – 2.79 (m, 2H), 1.78 – 1.46 (m, 3H). Rotamers present.

Example 181: (R)-(4-Fluoro-7-methyl-1H-benzo[d]imidazol-2-yl)(4-methyl-6,7-dihydrothiazolo[5,4-c]pyridin-5(4H)-yl)methanone



[00669] Step A: ((R)-(4-Fluoro-7-methyl-1H-benzo[d]imidazol-2-yl)(4-methyl-6,7-dihydrothiazolo[5,4-c]pyridin-5(4H)-yl)methanone was prepared from 4-fluoro-7-methyl-1H-benzo[d]imidazole-2-carboxylic acid (Example 42, Step C) and a mixture of (R)-4-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridine 2,2,2-trifluoroacetate and (R)-6-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridine 2,2,2-trifluoroacetate (Examples 170A and 170B, Step B) according to the procedure of Examples 168A and 168B, Step C. LC-MS: 331.2 [M+H]⁺. ¹H NMR (400 MHz, CD₃CN) δ 8.80 – 8.75 (m, 1H), 7.11 – 7.03 (m, 1H), 6.99 – 6.87 (m, 1H), 6.02 – 5.90 (m, 1H), 4.91 – 4.85 (m, 0.5H), 3.63 – 3.46 (m, 0.5H), 3.41 – 3.20 (m, 0.5H), 3.11 – 2.90 (m, 0.5H), 2.53 (s, 3H), 2.05 – 2.01 (m, 0.5H), 1.75 (d, J = 6.5 Hz, 1H), 1.58 (d, J = 6.7 Hz, 2H).

Example 182: trans-(7-Chloro-1H-benzo[d]imidazol-2-yl)((4R,6R)-2,4,6-trimethyl-6,7-dihydrothiazolo[5,4-c]pyridin-5(4H)-yl)methanone



[00670] Step A: trans-(4R,6R)-tert-Butyl 2-amino-4,6-dimethyl-6,7-dihydrothiazolo[5,4-c]pyridine-5(4H)-carboxylate was prepared from trans-(2R,6R)-tert-butyl 2,6-dimethyl-4-oxopiperidine-1-carboxylate according to Example 146, Step A. LC-MS: 284.4 [M+H]⁺.

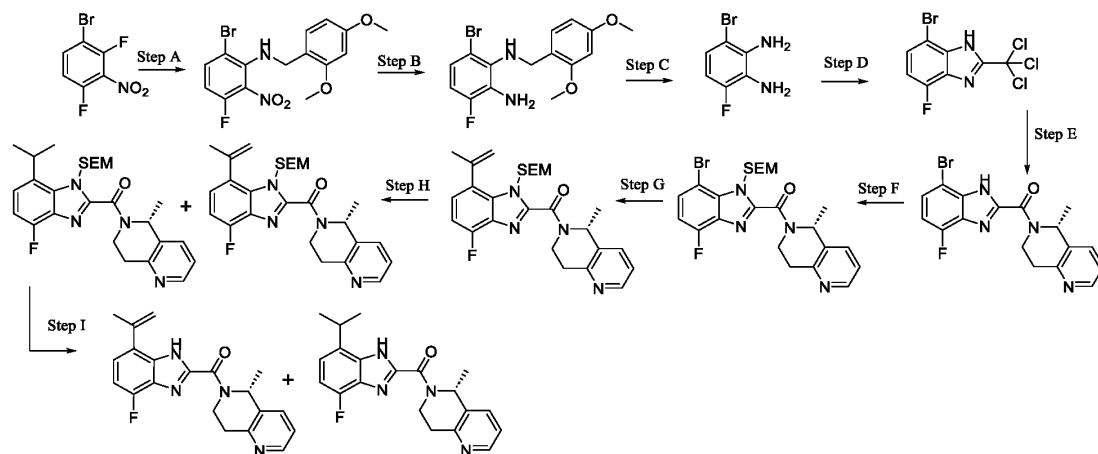
[00671] Step B: trans-(4R,6R)-tert-Butyl 2-bromo-4,6-dimethyl-6,7-dihydrothiazolo[5,4-c]pyridine-5(4H)-carboxylate was prepared from trans-(4R,6R)-tert-butyl 2-amino-4,6-dimethyl-6,7-dihydrothiazolo[5,4-c]pyridine-5(4H)-carboxylate according to Example 146, Step B. LC-MS: 349.4 [M+H]⁺.

[00672] Step C: trans-(4R,6R)-tert-Butyl 2,4,6-trimethyl-6,7-dihydrothiazolo[5,4-c]pyridine-5(4H)-carboxylate was prepared from trans-(4R,6R)-tert-butyl 2-bromo-4,6-dimethyl-6,7-dihydrothiazolo[5,4-c]pyridine-5(4H)-carboxylate according to Example 146, Step C. LC-MS: 284.4 [M+H]⁺.

[00673] Step D: trans-(4R,6R)-tert-Butyl 2,4,6-trimethyl-6,7-dihydrothiazolo[5,4-c]pyridine-5(4H)-carboxylate was prepared from trans-(4R,6R)-tert-butyl 2,4,6-trimethyl-6,7-dihydrothiazolo[5,4-c]pyridine-5(4H)-carboxylate according to Example 146, Step D. LC-MS: 183.2 [M+H]⁺.

[00674] Step E: trans-(7-Chloro-1H-benzo[d]imidazol-2-yl)((4R,6R)-2,4,6-trimethyl-6,7-dihydrothiazolo[5,4-c]pyridin-5(4H)-yl)methanone was prepared from trans-(4R,6R)-2,4,6-trimethyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridine according to Example 146, Step E. LC-MS: 361.5 [M+H]⁺. ¹H NMR (400 MHz, CD₃CN) δ 11.29 (br s, 1H), 7.63 – 7.51 (m, 1H), 7.37 (d, J = 7.6 Hz, 1H), 7.31 (t, J = 7.8 Hz, 1H), 6.44 – 6.16 (m, 1H), 5.73 – 5.42 (m, 1H), 3.17 – 3.02 (m, 1H), 2.95 (d, J = 13.7 Hz, 1H), 2.63 (s, 3H), 1.60 (d, J = 4.2 Hz, 3H), 1.28 – 1.08 (m).

Example 183: (R)-(4-Fluoro-7-(prop-1-en-2-yl)-1H-benzo[d]imidazol-2-yl)(5-methyl-7,8-dihydro-1,6-naphthyridin-6(5H)-yl)methanone and (R)-(4-Fluoro-7-isopropyl-1H-benzo[d]imidazol-2-yl)(5-methyl-7,8-dihydro-1,6-naphthyridin-6(5H)-yl)methanone



[00675] Step A: To a solution of 1-bromo-2,4-difluoro-3-nitrobenzene (8.40 mmol) in MeCN (33.6 mL) was added 2,4-dimethoxybenzylamine (1.29 mL, 8.40 mmol) and N,N-diisopropylethylamine (2.96 mL, 16.8 mmol). The reaction was stirred at room temperature for 45 min and then water was added. The solution was extracted with EtOAc, washed with brine, dried over anhydrous Na₂SO₄, filtered and concentrated. The crude material was purified by flash chromatography on silica gel using a solution of EtOAc in heptanes (0 to 10% gradient) to afford 6-bromo-N-(2,4-dimethoxybenzyl)-3-fluoro-2-nitroaniline.

[00676] Step B: To a solution of 6-bromo-N-(2,4-dimethoxybenzyl)-3-fluoro-2-nitroaniline (1.00 g, 2.60 mmol) in THF (10.4 mL) was added platinum on activated carbon (5% wt., 506 mg, 0.130 mmol) at 25 °C under H₂ (1 atm). The mixture was stirred at 25 °C for 3 d. The mixture was passed through a 0.45 μm PTFE filter. The filtrate was concentrated in vacuo to afford 6-

bromo-N1-(2,4-dimethoxybenzyl)-3-fluorobenzene-1,2-diamine. Used as-is in the next step without further purification. LC-MS: 355.0 [M+H]⁺.

[00677] Step C: A solution of 6-bromo-N1-(2,4-dimethoxybenzyl)-3-fluorobenzene-1,2-diamine (788 mg, 2.22 mmol) in TFA (4.44 mL) was stirred at room temperature for 1 h. The reaction was concentrated and co-evaporated with MeCN twice to afford 3-bromo-6-fluorobenzene-1,2-diamine. The crude was used as-is in the next step without further purification, assumed quantitative.

[00678] Step D: 7-Bromo-4-fluoro-2-(trichloromethyl)-1H-benzo[d]imidazole was prepared from 3-bromo-6-fluorobenzene-1,2-diamine (506.8 mg, 0.357 mmol) according to the procedure of Example 14, step A. The compound was used without further purification. LC-MS: 332.9 [M+H]⁺.

[00679] Step E: (R)-(7-Bromo-4-fluoro-1H-benzo[d]imidazol-2-yl)(5-methyl-7,8-dihydro-1,6-naphthyridin-6(5H)-yl)methanone was prepared from 7-bromo-4-fluoro-2-(trichloromethyl)-1H-benzo[d]imidazole according to the procedure of Example 148A, step C. LC-MS: 391.1 [M+H]⁺. ¹H NMR (500 MHz, DMSO) δ 14.32 – 13.78 (m, 1H), 8.41 (ddd, J = 11.6, 4.7, 1.2 Hz, 1H), 7.81 – 7.60 (m, 1H), 7.55 – 7.46 (m, 1H), 7.31 – 7.20 (m, 1H), 7.21 – 7.02 (m, 1H), 6.12 – 5.58 (m, 1H), 5.31 – 4.62 (m, 1H), 3.76 – 3.40 (m, 1H), 3.23 – 3.09 (m, 1H), 3.06 – 2.89 (m, 1H), 1.74 – 1.54 (m, 3H).

[00680] Step F: (R)-(7-Bromo-4-fluoro-1H-benzo[d]imidazol-2-yl)(5-methyl-7,8-dihydro-1,6-naphthyridin-6(5H)-yl)methanone (200 mg, 0.514 mmol) was suspended in THF (5.14 mL) under nitrogen and cooled to 0°C. NaH (60% in oil, 22.6 mg, 0.565 mmol) was added and the reaction was allowed to stir for 15 min. at 0°C. The reaction was treated with (2-chloromethoxyethyl)trimethylsilane (131 uL, 0.668 mmol) and stirred overnight at room temperature. The reaction was diluted with ethyl acetate and saturated aqueous NH₄Cl. The layers were separated, and the aqueous layer was washed with more EtOAc. The combined organic layers were dried over anhydrous Na₂SO₄ and concentrated in vacuo. The crude material was purified by flash chromatography on silica gel using a solution of EtOAc in heptanes (20 to 80% gradient) to afford (R)-(7-bromo-4-fluoro-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-benzo[d]imidazol-2-yl)(5-methyl-7,8-dihydro-1,6-naphthyridin-6(5H)-yl)methanone. LC-MS: 519.3/521.1 [M+H]⁺.

[00681] Step G: Into a round-bottom flask under nitrogen, was placed (R)-(7-bromo-4-fluoro-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-benzo[d]imidazol-2-yl)(5-methyl-7,8-dihydro-1,6-naphthyridin-6(5H)-yl)methanone (45.0 mg, 0.0866 mmol), dioxane (525 uL), water (52.5 uL), isopropenylboronic acid pinacol ester (51.4 uL, 0.260 mmol), cesium carbonate (87.8 mg, 0.264

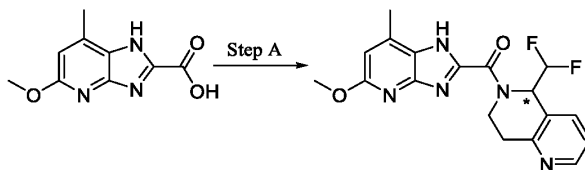
mmol), and [1,1'-Bis(diphenylphosphino)ferrocene]dichloropalladium(II), complex with dichloromethane (7.07 mg, 0.00866 mmol). The resulting solution was stirred for 4 h at 70 °C and then cooled to room temperature. The reaction was filtered through a celite, washed with EtOAc, and the filtrate was concentrated. The crude material was purified by flash chromatography on silica gel to afford (R)-(4-fluoro-7-(prop-1-en-2-yl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-benzo[d]imidazol-2-yl)(5-methyl-7,8-dihydro-1,6-naphthyridin-6(5H)-yl)methanone. LC-MS: 481.3 [M+H]⁺.

[00682] Step H: To a solution of (R)-(4-fluoro-7-(prop-1-en-2-yl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-benzo[d]imidazol-2-yl)(5-methyl-7,8-dihydro-1,6-naphthyridin-6(5H)-yl)methanone (40.0 mg, 0.0832 mmol) in MeOH (832 uL) was added palladium on carbon (10% wt., 17.7 mg, 0.0166 mmol). Hydrogen was bubbled through the reaction for 10 min then the reaction was stirred at room temperature for 45 min. The reaction was passed through a 0.45 µm PTFE filter and concentrated to afford a mixture of (R)-(4-fluoro-7-isopropyl-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-benzo[d]imidazol-2-yl)(5-methyl-7,8-dihydro-1,6-naphthyridin-6(5H)-yl)methanone and (R)-(4-fluoro-7-(prop-1-en-2-yl)-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-benzo[d]imidazol-2-yl)(5-methyl-7,8-dihydro-1,6-naphthyridin-6(5H)-yl)methanone. The resulting crude material was used without further purification. LC-MS: 483.4 and 481.4 [M+H]⁺.

[00683] Step I: A solution of (R)-(4-fluoro-7-isopropyl-1-((2-(trimethylsilyl)ethoxy)methyl)-1H-benzo[d]imidazol-2-yl)(5-methyl-7,8-dihydro-1,6-naphthyridin-6(5H)-yl)methanone (40.2 mg, 0.0833 mmol) in TFA (416 uL) was stirred at room temperature for 4 h. The reaction was concentrated and co-evaporated with DCM twice. The crude was purified by semi-prep HPLC-MS (Column: CSH Prep C18 OBD, 5 µm, 30 x 75 mm. Gradient: isocratic at 30% B for 1 min, 30% to 50% B in 8 min, 50% to 100% B in 0.1 min, hold 100% B for 2.9 min. Eluents: A = Milli Q H₂O + 10 mM ammonium formate pH = 3.8; B = MeCN. Solvent at 40 °C. Flow: 45 mL/min. Run Time: 12 min). The tubes with the desired products were combined, concentrated and lyophilized to afford (R)-(4-fluoro-7-(prop-1-en-2-yl)-1H-benzo[d]imidazol-2-yl)(5-methyl-7,8-dihydro-1,6-naphthyridin-6(5H)-yl)methanone and (R)-(4-fluoro-7-isopropyl-1H-benzo[d]imidazol-2-yl)(5-methyl-7,8-dihydro-1,6-naphthyridin-6(5H)-yl)methanone. (R)-(4-fluoro-7-(prop-1-en-2-yl)-1H-benzo[d]imidazol-2-yl)(5-methyl-7,8-dihydro-1,6-naphthyridin-6(5H)-yl)methanone. LC-MS: 351.4 [M+H]⁺. ¹H NMR (500 MHz, DMSO) δ 8.40 (dd, J = 12.8, 4.2 Hz, 1H), 7.82 – 7.56 (m, 1H), 7.30 – 7.18 (m, 2H), 7.11 – 7.03 (m, 1H), 6.12 – 5.62 (m, 1H), 5.35 (s, 1H), 5.10 – 4.68 (m, 1H), 3.74 – 3.59 (m, 1H), 3.23 – 3.18 (m, 1H), 3.01 – 2.90 (m, 1H), 2.26 (s, 3H), 1.73 – 1.54 (m, 3H). 2 protons not apparent. (R)-(4-fluoro-7-isopropyl-1H-

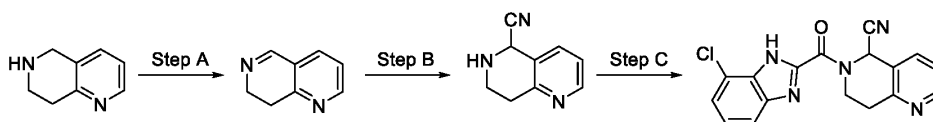
benzo[d]imidazol-2-yl)(5-methyl-7,8-dihydro-1,6-naphthyridin-6(5H)-yl)methanone. LC-MS: 353.4 $[M+H]^+$. 1H NMR (500 MHz, DMSO) δ 13.38 (br s, 1H), 8.47 – 8.37 (m, 1H), 7.82 – 7.61 (m, 1H), 7.30 – 7.20 (m, 1H), 7.14 – 7.07 (m, 1H), 7.07 – 6.99 (m, 1H), 6.23 – 5.70 (m, 1H), 5.34 – 4.71 (m, 1H), 3.74 – 3.61 (m, 1H), 3.57 – 3.47 (m, 1H), 3.23 – 3.14 (m, 1H), 3.02 – 2.94 (m, 1H), 1.71 – 1.55 (m, 3H), 1.30 (d, J = 6.5 Hz, 6H).

Example 184: (R) or (S)-(5-(Difluoromethyl)-7,8-dihydro-1,6-naphthyridin-6(5H)-yl)(5-methoxy-7-methyl-1H-imidazo[4,5-b]pyridin-2-yl)methanone



[00684] Step A: (R) or (S)-(5-(Difluoromethyl)-7,8-dihydro-1,6-naphthyridin-6(5H)-yl)(5-methoxy-7-methyl-1H-imidazo[4,5-b]pyridin-2-yl)methanone was prepared from 5-methoxy-7-methyl-1H-imidazo[4,5-b]pyridine-2-carboxylic acid and (R) or (S)-5-(difluoromethyl)-5,6,7,8-tetrahydro-1,6-naphthyridine (single enantiomer with the absolute stereochemistry unassigned) (Example 123, step H) according to the procedure of Example 115, Step E. LC-MS: 374.2 $[M+H]^+$. 1H NMR (400 MHz, DMSO- d_6) δ 13.61 (bs, 1H), 8.53 (ad, J = 4.7 Hz, 1H), 8.00 – 7.76 (m, 1H), 7.55 – 7.20 (m, 1H), 6.94 – 6.30 (m, 2H), 6.19 – 4.62 (m, 1H), 3.96 – 3.81 (m, 4H), 3.53 – 2.96 (m, 3H), 2.54 (d, J = 6.1 Hz, 3H). Example 184 is a single enantiomer with the absolute stereochemistry unassigned.

Example 185: 6-(7-Chloro-1H-benzo[d]imidazole-2-carbonyl)-5,6,7,8-tetrahydro-1,6-naphthyridine-5-carbonitrile



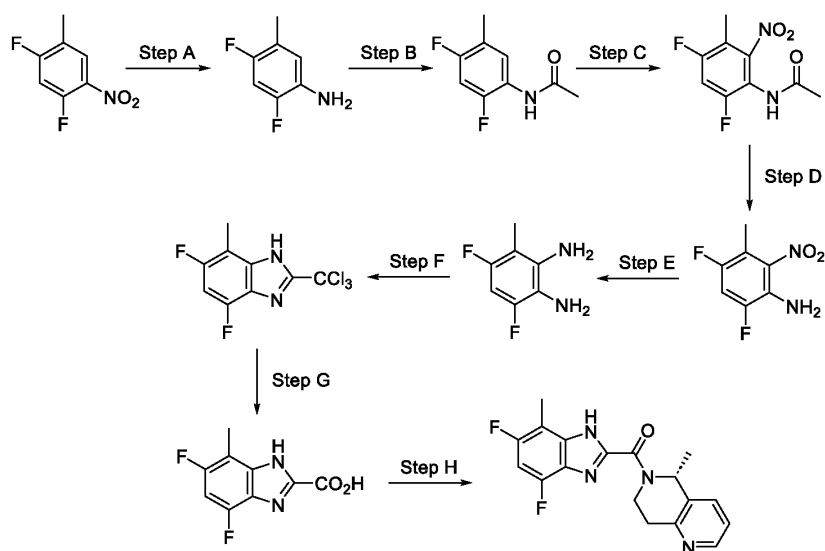
[00685] Step A: To a solution of 5,6,7,8-tetrahydro-1,6-naphthyridine (200 mg, 1.49 mmol, 1.0 eq) in DCM (32 mL)/DMSO (0.32 mL) was added manganese dioxide (2.39 g, 27.46 mmol, 18 eq). The mixture was stirred at 20 °C for 12 h. The mixture was filtered through Celite pad, then it was dried to give 7,8-dihydro-1,6-naphthyridine. LCMS: 133.2 $[M+H]^+$. 1H NMR (400 MHz, $CDCl_3$) δ 8.53 (dd, J = 1.6, 5.0 Hz, 1H), 8.35 (s, 1H), 7.56 (dd, J = 1.6, 7.5 Hz, 1H), 7.27 – 7.23 (m, 1H), 3.95 (dt, J = 2.1, 7.9 Hz, 2H), 3.02 – 2.91 (m, 2H).

[00686] Step B: To a solution of 7,8-dihydro-1,6-naphthyridine (200 mg, 1.51 mmol, 1.0 eq) in $CHCl_3$ (10 mL) was added 4A molecular sieves (200 mg) and trimethylsilyl cyanide (300 mg, 3.03 mmol, 2.0 eq). The mixture was stirred at 20 °C for 2 h under N_2 atmosphere. The reaction

mixture was allowed to cool to room temperature, poured into water (10 mL) and extracted with DCM (10 mL x 4). The combined organic layers were dried over Na₂SO₄, filtered, and concentrated under vacuum to give a residue which was purified by flash silica gel chromatography using a gradient of EtOAc/petroleum ether from 0/1 to 7/10. The residue was lyophilization with HCl (1 M, 0.1 mL) to give 5,6,7,8-tetrahydro-1,6-naphthyridine-5-carbonitrile. LCMS: 160.2 [M+H]⁺. ¹H NMR (400 MHz, CDCl₃) δ 8.88 – 8.79 (m, 1H), 8.55 (dd, *J* = 1.4, 8.1 Hz, 1H), 7.94 (dd, *J* = 5.6, 8.1 Hz, 1H), 4.91 – 4.90 (m, 1H), 3.69 (dt, *J* = 1.5, 6.2 Hz, 2H), 3.39 (t, *J* = 6.2 Hz, 2H).

[00687] Step C: A mixture of 5,6,7,8-tetrahydro-1,6-naphthyridine-5-carbonitrile (60 mg, 377 μmol, 1.0 eq), 7-chloro-1*H*-benzimidazole-2-carboxylic acid (74.1 mg, 377 μmol, 1.0 eq), HATU (71.7 mg, 188 μmol, 0.5 eq) and DIEA (146 mg, 1.13 mmol, 197 μL, 3.0 eq) in DMF (1.0 mL) was stirred at 20 °C for 1 h. The reaction mixture was poured into H₂O (2.0 mL) and extracted with EtOAc (3.0 mL x 3). The combined organic layers were dried over Na₂SO₄, filtered, and concentrated under vacuum to give a residue which was purified by preparative HPLC (Phenomenex Luna C18 column (100 × 40 mm, 5 μm); flow rate: 25 mL/min; gradient: 15% – 45% B over 8 min; mobile phase A: 0.04% aqueous HCl, mobile phase B: acetonitrile). 6-(7-Chloro-1*H*-benzo[*d*]imidazole-2-carbonyl)-5,6,7,8-tetrahydro-1,6-naphthyridine-5-carbonitrile hydrochloride was obtained. LCMS: 338.1 [M+H]⁺. ¹H NMR (400 MHz, CDCl₃) δ 8.76 (br s, 1H), 8.55 (br d, *J* = 8.3 Hz, 1H), 7.96 – 7.80 (m, 1H), 7.71 – 7.57 (m, 1H), 7.49 – 7.24 (m, 2H), 6.26 – 5.02 (m, 1H), 4.88 (s, 2H), 3.97 – 3.52 (m, 2H).

Example 186: (R)-(4,6-Difluoro-7-methyl-1*H*-benzo[*d*]imidazol-2-yl)(5-methyl-7,8-dihydro-1,6-naphthyridin-6(5*H*)-yl)methanone



[00688] Step A: To a solution of 1,5-difluoro-2-methyl-4-nitrobenzene (800 mg, 4.62 mmol) in EtOH (24.0 mL) and H₂O (8.00 mL) was added iron powder (2.06 g, 37.0 mmol) and ammonium chloride (1.98 g, 37.0 mmol). The mixture was stirred at 80 °C for 12 h. The reaction mixture was filtered and the filtrate was concentrated under vacuum to give 2,4-difluoro-5-methylaniline. ¹H NMR (400 MHz, DMSO-*d*₆) δ 6.92 (dd, *J* = 9.8, 11.3 Hz, 1H), 6.61 (dd, *J* = 8.4, 9.7 Hz, 1H), 4.88 (br s, 2H), 2.10 – 2.05 (m, 3H).

[00689] Step B: To a solution of 2,4-difluoro-5-methylaniline (500 mg, 3.49 mmol) in DCM (20.0 mL) was added acetic anhydride (428 mg, 4.19 mmol) and TEA (1.06 g, 10.5 mmol). The mixture was stirred at 25 °C for 12 h. The reaction mixture was poured into H₂O (20 mL) and extracted with DCM (20.0 mL x 3). The combined organic layers were dried over Na₂SO₄, filtered, and concentrated under vacuum to give a residue which was purified by flash silica gel chromatography using a gradient of petroleum/EtOAc ether from 30/1 to 19/1 to give N-(2,4-difluoro-5-methylphenyl)acetamide. LC-MS: 186.5 [M+H]⁺.

[00690] Step C: To a solution of N-(2,4-difluoro-5-methylphenyl)acetamide (350 mg, 1.89 mmol) in H₂SO₄ (6.00 mL) was added HNO₃ (595 mg, 9.45 mmol). The mixture was stirred at 0 °C for 1 h. The reaction mixture was poured into water. The precipitate was collected by filtration and dried *in vacuo* to give crude product. N-(4,6-difluoro-3-methyl-2-nitrophenyl)acetamide. LC-MS: 231.4 [M+H]⁺.

[00691] Step D: To a solution of N-(4,6-difluoro-3-methyl-2-nitrophenyl)acetamide (350 mg, 1.52 mmol) in MeOH (4.00 mL) was added HCl aqueous (2M, 3.80 mL). The mixture was stirred at 70 °C for 12 h. The reaction mixture was poured into H₂O (10.0 mL) and extracted with EtOAc (30.0 mL x 3). The combined organic layers were dried over Na₂SO₄, filtered, and concentrated under vacuum to give a residue which was purified by flash silica gel chromatography using a gradient of petroleum/EtOAc ether from 30/1 to 19/1 to give 4,6-difluoro-3-methyl-2-nitroaniline. LC-MS: 187.5 [M-H]⁻. ¹H NMR (400 MHz, DMSO-*d*₆) δ 7.47 (dd, *J* = 9.6, 11.2 Hz, 1H), 6.72 – 5.41 (m, 2H), 2.15 (dd, *J* = 1.2, 2.3 Hz, 3H).

[00692] Step E: To a solution of 4,6-difluoro-3-methyl-2-nitroaniline (130 mg, 0.691 mmol) in EtOH (6.00 mL) and H₂O (2.00 mL) was added iron powder (309 mg, 5.53 mmol) and ammonium chloride (296 mg, 5.53 mmol). The mixture was stirred at 80 °C for 12 h. The reaction mixture was filtered and concentrated under reduced pressure to give 4,6-difluoro-3-methylbenzene-1,2-diamine. LC-MS: 157.1 [M-H]⁻.

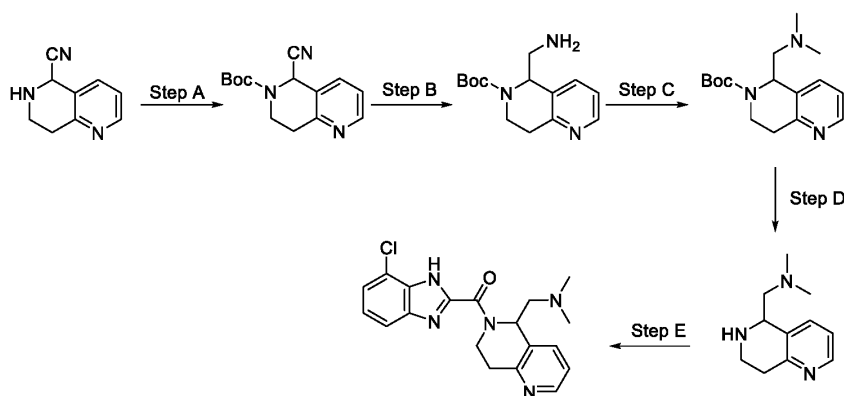
[00693] Step F: To a solution of 4,6-difluoro-3-methylbenzene-1,2-diamine (100 mg, 0.632 mmol) in HOAc (2.00 mL) was added methyl 2,2,2-trichloroethanimidate (112 mg, 0.632 mmol). The mixture was stirred at 25 °C for 1 h. The reaction mixture was filtered. The filter

cake was washed with H₂O (2.00 mL), and dried under reduced pressure to give 4,6-difluoro-7-methyl-2-(trichloromethyl)-1H-benzo[d]imidazole. LC-MS: 285.1 [M+H]⁺.

[00694] Step G: A solution of 4,6-difluoro-7-methyl-2-(trichloromethyl)-1H-benzo[d]imidazole (70 mg, 0.245 mmol) and NaOH (2M aqueous, 7.00 mL) was stirred at 25 °C for 1 h. The mixture was adjusted to pH 5 – 6 with HCl (6M aqueous). The resulting precipitate was filtered and the filter cake was dried under vacuum to give 4,6-difluoro-7-methyl-1H-benzo[d]imidazole-2-carboxylic acid. LC-MS: 213.2 [M+H]⁺.

[00695] Step H: To a solution of 4,6-difluoro-7-methyl-1H-benzo[d]imidazole-2-carboxylic acid (35.0 mg, 0.165 mmol) in DMF (1.00 mL) was added (R)-5-methyl-5,6,7,8-tetrahydro-1,6-naphthyridine (30.5 mg, 0.165 mmol), DIEA (42.6 mg, 0.330 mmol) and HATU (31.4 mg, 0.082 mmol). The mixture was stirred at 25 °C for 1 h. The reaction mixture was poured into H₂O (2.00 mL) and extracted with EtOAc (1.00 mL x 3). The combined organic layers were dried over Na₂SO₄, filtered, and concentrated under vacuum to give a residue which was purified by prep-HPLC (Phenomenex luna C18 column (100 × 40 mm, 5 μm); flow rate: 25 mL/min; gradient: 10% – 40% B over 8 min; mobile phase A: H₂O (0.04% HCl), mobile phase B: acetonitrile). (R)-(4,6-difluoro-7-methyl-1H-benzo[d]imidazol-2-yl)(5-methyl-7,8-dihydro-1,6-naphthyridin-6(5H)-yl)methanone. LC-MS: 343.1 [M+H]⁺. ¹H NMR (400 MHz, DMSO-*d*₆) δ 14.01 – 13.40 (m, 1H), 8.83 – 8.53 (m, 1H), 8.47 – 7.99 (m, 1H), 7.84 – 7.51 (m, 1H), 7.29 – 7.05 (m, 1H), 6.58 – 5.76 (m, 1H), 5.61 – 4.53 (m, 1H), 3.74 – 3.67 (m, 1H), 3.22 – 3.14 (m, 2H), 2.45 – 2.41 (m, 3H), 1.79 – 1.55 (m, 3H).

Example 187: 7-Chloro-1H-benzo[d]imidazol-2-yl)(5-((dimethylamino)methyl)-7,8-dihydro-1,6-naphthyridin-6(5H)-yl)methanone



[00696] Step A: To a solution of 5,6,7,8-tetrahydro-1,6-naphthyridine-5-carbonitrile (Example 201, step B) (500 mg, 3.14 mmol) in CHCl₃ (10.0 mL) was added di-tert-butyl dicarbonate (822 mg, 3.77 mmol) and TEA (635 mg, 6.28 mmol). The mixture was stirred at 20 °C for 12 h. The

reaction mixture was added to H₂O (15.0 mL) and extracted with EtOAc (15.0 mL x 3). The combined organic layers were dried over Na₂SO₄, filtered and concentrated under reduced pressure to give a residue which was purified by flash silica gel chromatography using a gradient of EtOAc/petroleum ether from 1/100 to 1/10 to give tert-butyl 5-cyano-7,8-dihydro-1,6-naphthyridine-6(5H)-carboxylate LC-MS: 260.2 [M+H]⁺. ¹H NMR (400 MHz, CDCl₃) δ 8.58 (br d, *J* = 3.9 Hz, 1H), 7.67 (d, *J* = 7.8 Hz, 1H), 7.27 (s, 1H), 6.27 – 5.75 (m, 1H), 4.69 – 4.18 (m, 1H), 3.56 – 3.27 (m, 1H), 3.21 – 2.92 (m, 2H), 1.59 – 1.51 (m, 9H).

[00697] Step B: To a solution of Raney-Ni (66.1 mg, 0.771 mmol) in MeOH (20.0 mL) was added ammonium hydroxide (910 mg, 7.79 mmol) and tert-butyl 5-cyano-7,8-dihydro-5H-1,6-naphthyridine-6-carboxylate (200 mg, 0.771 mmol). The mixture was stirred at 20 °C for 12 h under H₂ (15 Psi). The reaction mixture was filtered through Celite pad, and the filtrate was concentrated *in vacuo* to give tert-butyl 5-(aminomethyl)-7,8-dihydro-1,6-naphthyridine-6(5H)-carboxylate. LC-MS: 264.2 [M+H]⁺.

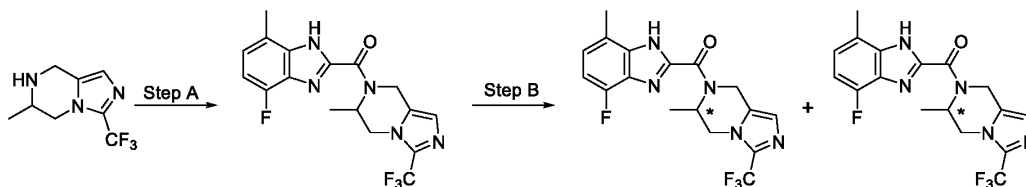
[00698] Step C: To a solution of tert-butyl 5-(aminomethyl)-7,8-dihydro-1,6-naphthyridine-6(5H)-carboxylate (100 mg, 0.380 mmol) and formaldehyde (154 mg, 1.90 mmol) in MeOH (2.00 mL), was added acetic acid (2.28 mg, 0.038 mmol) to adjust pH=5-6, then sodium cyanoborohydride (47.7 mg, 0.759 mmol) was added. The mixture was stirred at 25 °C for 2 h. The reaction mixture was poured into H₂O (2.00 mL) and extracted with EtOAc (1.00 mL x 3). The combined organic layers were washed with brine (1.00 mL x 3), dried over Na₂SO₄, filtered, and concentrated *in vacuo* to give a residue. It was further purified by preparative TLC (pure EtOAc, *R_f* = 0.3). tert-butyl 5-((dimethylamino)methyl)-7,8-dihydro-1,6-naphthyridine-6(5H)-carboxylate was obtained. LC-MS: 292.4 [M+H]⁺. ¹H NMR (400 MHz, CDCl₃) δ 8.42 (br d, *J* = 2.3 Hz, 1H), 7.63 – 7.51 (m, 1H), 7.12 (dd, *J* = 4.8, 7.8 Hz, 1H), 3.49 (s, 1H), 3.39 – 2.55 (m, 5H), 2.47 (dd, *J* = 6.7, 12.7 Hz, 1H), 2.35 (br d, *J* = 11.5 Hz, 6H), 1.50 (s, 9H).

[00699] Step D: A solution of tert-butyl 5-((dimethylamino)methyl)-7,8-dihydro-1,6-naphthyridine-6(5H)-carboxylate (60.0 mg, 0.206 mmol) in HCl/EtOAc (4M, 1.00 mL) was stirred at 25 °C for 1.5 h. The mixture was concentrated under reduced pressure to give N,N-dimethyl-1-(5,6,7,8-tetrahydro-1,6-naphthyridin-5-yl)methanamine. LC-MS: 192.3 [M+H]⁺. ¹H NMR (400 MHz, DMSO-*d*₆) δ 8.56 (d, *J* = 3.5 Hz, 1H), 7.87 (br d, *J* = 6.4 Hz, 1H), 7.47 – 7.38 (m, 1H), 5.33 – 5.07 (m, 1H), 4.05 – 3.85 (m, 1H), 3.15 – 2.84 (m, 9H), 2.46 – 2.35 (m, 3H).

[00700] Step E: To a solution of N,N-dimethyl-1-(5,6,7,8-tetrahydro-1,6-naphthyridin-5-yl)methanamine (26.0 mg, 0.136 mmol) in DMF (0.50 mL) was added 7-chloro-1H-benzimidazole-2-carboxylic acid (26.7 mg, 0.136 mmol), DIEA (35.1 mg, 0.272 mmol) and HATU (25.8 mg, 0.068 mmol). The mixture was stirred at 25 °C for 30 min. The reaction

mixture was poured into H₂O (2.00 mL) and extracted with EtOAc (1.00 mL x 3). The combined organic layers were dried over Na₂SO₄, filtered, and concentrated under vacuum to give a residue which was purified by preparative HPLC (Waters Xbridge Prep OBD C18 column (150 × 40 mm, 10 mm); flow rate: 60 mL/min; gradient: 5% – 50% B over 8 min; mobile phase A: H₂O (10mM NH₄HCO₃), mobile phase B: acetonitrile). (7-chloro-1H-benzo[d]imidazol-2-yl)(5-((dimethylamino)methyl)-7,8-dihydro-1,6-naphthyridin-6(5H)-yl)methanone was obtained. LC-MS: 370.1 [M+H]⁺; ¹H NMR (400 MHz, DMSO-*d*₆) δ 13.92 – 13.16 (m, 1H), 8.43 (t, *J* = 4.8 Hz, 1H), 7.82 – 7.46 (m, 2H), 7.42 – 7.21 (m, 3H), 6.73 – 5.68 (m, 1H), 4.85 – 3.68 (m, 1H), 3.20 – 2.65 (m, 5H), 2.30 (s, 3H), 2.03 (s, 3H).

Examples 188A and 188B: (R) or (S)-(4-Fluoro-7-methyl-1H-benzo[d]imidazol-2-yl)(6-methyl-3-(trifluoromethyl)-5,6-dihydroimidazo[1,5-a]pyrazin-7(8H)-yl)methanone and (R) or (S)-(4-Fluoro-7-methyl-1H-benzo[d]imidazol-2-yl)(6-methyl-3-(trifluoromethyl)-5,6-dihydroimidazo[1,5-a]pyrazin-7(8H)-yl)methanone

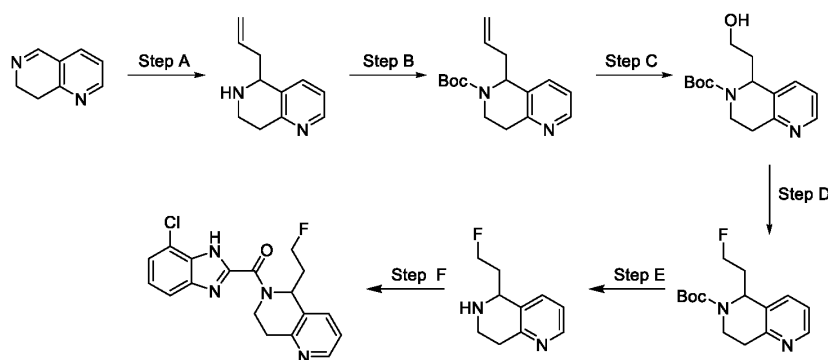


[00701] Step A: To a solution of 6-methyl-3-(trifluoromethyl)-5,6,7,8-tetrahydroimidazo[1,5-a]pyrazine (100 mg, 0.487 mmol) and 4-fluoro-7-methyl-1H-benzo[d]imidazole-2-carboxylic acid (189 mg, 0.975 mmol) in DMF (1.50 mL) was added DIEA (189 mg, 1.46 mmol) and HATU (185 mg, 0.487 mmol). The mixture was stirred at 20 °C for 1 h. The mixture was poured into water (15.0 mL) and extracted with EtOAc (15.0 mL x 3). The combined organic layers were dried over Na₂SO₄, filtered, and concentrated under vacuum to give a residue which was purified by flash silica gel chromatography using a gradient of EtOAc/petroleum ether from 0/1 to 1/1 to give ((4-fluoro-7-methyl-1H-benzo[d]imidazol-2-yl)(6-methyl-3-(trifluoromethyl)-5,6-dihydroimidazo[1,5-a]pyrazin-7(8H)-yl)methanone. LC-MS: 382.2 [M+H]⁺.

[00702] Step B: ((4-Fluoro-7-methyl-1H-benzo[d]imidazol-2-yl)(6-methyl-3-(trifluoromethyl)-5,6-dihydroimidazo[1,5-a]pyrazin-7(8H)-yl)methanone (100 mg, 0.262 mmol) was further separation by chiral SFC ((DAICEL CHIRALPAK AD (250 × 30 mm, 10 μm); flow rate: 70 mL/min; gradient: 25 – 25% B over 13 min; mobile phase A: CO₂, mobile phase B: IPA(0.1%NH₃H₂O)). Enantiomer A: (R) or (S)-(4-Fluoro-7-methyl-1H-benzo[d]imidazol-2-yl)(6-methyl-3-(trifluoromethyl)-5,6-dihydroimidazo[1,5-a]pyrazin-7(8H)-yl)methanone was obtained. LC-MS: 382.1 [M+H]⁺; ¹H NMR (400 MHz, CDCl₃) δ 11.13 – 10.32 (m, 1H), 7.12 –

6.70 (m, 4H), 5.50 – 5.14 (m, 1H), 4.80 – 4.54 (m, 1H), 4.45 – 4.22 (m, 2H), 2.70 – 2.39 (m, 3H), 1.45 – 1.21 (m, 3H). Enantiomer B: (R) or (S)-(4-Fluoro-7-methyl-1H-benzo[d]imidazol-2-yl)(6-methyl-3-(trifluoromethyl)-5,6-dihydroimidazo[1,5-a]pyrazin-7(8H)-yl)methanone was obtained. LC-MS: 382.1 [M+H]⁺. ¹H NMR (400 MHz, CDCl₃) δ 11.19 – 10.49 (m, 1H), 7.18 – 6.54 (m, 4H), 5.59 – 5.13 (m, 1H), 4.78 – 4.58 (m, 1H), 4.45 – 4.19 (m, 2H), 2.75 – 2.39 (m, 3H), 1.46 – 1.28 (m, 3H). The absolute stereochemistry for Enantiomer A and Enantiomer B was not determined.

Example 189: (7-Chloro-1H-benzo[d]imidazol-2-yl)(5-(2-fluoroethyl)-7,8-dihydro-1,6-naphthyridin-6(5H)-yl)methanone



[00703] Step A: To a small reaction vessel, iron (II) chloride (5.48 mg, 0.060 mmol), 1,2-bis(diphenylphosphanyl)benzene (19.2 mg, 0.043 mmol) and THF (2.50 mL) were added. The resulting mixture were sealed and stirred for 0.5 h at 20 °C to afford a homogeneous and green solution, which was then ready to be used as a catalyst. To a Schlenk reaction tube containing MeOH (274 mg, 8.55 mmol) and THF (2.50 mL) was added the catalyst solution prepared above, 7,8-dihydro-1,6-naphthyridine (250 mg, 1.89 mmol), and potassium allyl(trifluoro)boranuide (305 mg, 2.06 mmol). The reaction vessel was then sealed and the contents were stirred at 80 °C for 12 h. The reaction mixture was poured into H₂O (20.0 mL) and extracted with EtOAc (30.0 mL x 3). The combined organic layers were dried over Na₂SO₄, filtered and concentrated under reduced pressure to give 5-allyl-5,6,7,8-tetrahydro-1,6-naphthyridine. LC-MS: 175.2 [M+H]⁺.

[00704] Step B: To a solution of 5-allyl-5,6,7,8-tetrahydro-1,6-naphthyridine (500 mg, 2.87 mmol) in MeOH (10.0 mL) was added di-tert-butyl dicarbonate (689 mg, 3.16 mmol) and potassium carbonate (595 mg, 4.30 mmol). The mixture was stirred at 20 °C for 1 h. The reaction mixture was poured into H₂O (10.0 mL) and extracted with DCM (10.0 mL x 4). The combined organic layers were dried over Na₂SO₄, filtered and concentrated under vacuum to give a residue which was purified by flash silica gel chromatography using a gradient of EtOAc/petroleum

ether from 1/100 to 1/5 to give tert-butyl 5-allyl-7,8-dihydro-5H-1,6-naphthyridine-6-carboxylate. LC-MS: 275.3 [M+H]⁺.

[00705] Step C: A solution of tert-butyl 5-allyl-7,8-dihydro-5H-1,6-naphthyridine-6-carboxylate (270 mg, 0.984 mmol) and p-toluenesulfonic acid (18.7 mg, 0.098 mmol) in a mixture of DCM (12.5 mL) and MeOH (25.0 mL) at -78 °C was bubbled with O₃ until the blue color persisted (30 minutes). The excess of ozone was removed by bubbling through oxygen gas for 10 minutes. Then sodium borohydride (112 mg, 2.95 mmol) was added and the mixture was allowed to warm to 0 °C. After stirring 1 h. The reaction mixture was poured into H₂O (30.0 mL) and extracted with EtOAc (30.0 mL x 3). The combined organic layers were washed with brine (1.00 mL x 3), dried over Na₂SO₄, filtered and concentrated under reduced pressure to give a residue which was purified by flash silica gel chromatography using a gradient of EtOAc/petroleum ether from 1/100 to 1/1 to give tert-butyl 5-(2-hydroxyethyl)-7,8-dihydro-1,6-naphthyridine-6(5H)-carboxylate. LC-MS: 279.3 [M+H]⁺.

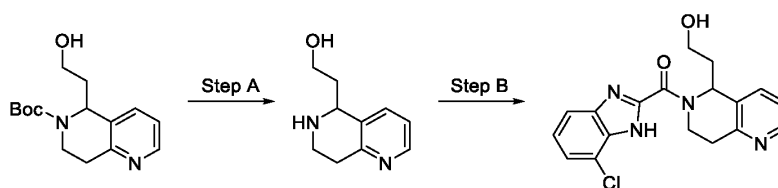
[00706] Step D: To a solution of tert-butyl 5-(2-hydroxyethyl)-7,8-dihydro-5H-1,6-naphthyridine-6-carboxylate (30.0 mg, 0.108 mmol) in THF (2.50 mL) was added TBAF (1M, 0.33 mL), 4-methylbenzenesulfonyl fluoride (36.4 mg, 0.209 mmol) and 4A MS (500 mg, 0.108 mmol). The mixture was stirred at 70 °C for 1 h. The reaction mixture was filtered then poured into sat. NaHCO₃ aqueous (10 mL) and extracted with EtOAc (5.00 mL x 3). The combined organic layers were washed with brine (5.00 mL x 2), dried over Na₂SO₄, filtered and concentrated under reduced pressure to give a residue. The residue was purified by prep-TLC (SiO₂, Petroleum ether/Ethyl acetate=0/1) to give tert-butyl 5-(2-fluoroethyl)-7,8-dihydro-5H-1,6-naphthyridine-6-carboxylate. LC-MS: 281.2 [M+H]⁺. ¹H NMR (400 MHz, CDCl₃) δ 8.45 (br d, *J* = 3.0 Hz, 1H), 7.47 (br d, *J* = 8.0 Hz, 1H), 7.20 – 7.14 (m, 1H), 5.48 – 5.27 (m, 1H), 4.71 – 4.37 (m, 2H), 4.26 – 4.18 (m, 1H), 3.36 – 3.25 (m, 1H), 3.36 – 3.05 (m, 1H), 2.99 – 2.81 (m, 1H), 2.22 – 2.11 (m, 1H), 1.86 – 1.74 (m, 1H), 1.50 (s, 9H).

[00707] Step E: To a solution of tert-butyl 5-(2-fluoroethyl)-7,8-dihydro-5H-1,6-naphthyridine-6-carboxylate (20 mg, 0.071 mmol) in EtOAc (1.00 mL) was added HCl/EtOAc (4M, 4.00 mL). The resulting mixture was stirred at 20 °C for 1 h. The mixture was concentrated under reduced pressure to give 5-(2-fluoroethyl)-5,6,7,8-tetrahydro-1,6-naphthyridine. LC-MS: 181.3 [M+H]⁺.

[00708] Step F: A mixture of 7-chloro-1H-benzimidazole-2-carboxylic acid (10 mg, 0.051 mmol), 5-(2-fluoroethyl)-5,6,7,8-tetrahydro-1,6-naphthyridine (13.2 mg, 0.061 mmol), HATU (19.3 mg, 0.051 mmol) and DIEA (19.7 mg, 0.153 mmol) in DMF (0.50 mL) was stirred at 20 °C for 1 h. The reaction mixture was poured into H₂O (2.00 mL) and extracted with EtOAc (3.00 mL x 3). The combined organic layers were dried over Na₂SO₄, filtered, and concentrated under

vacuum to give a residue which was purified by preparative HPLC (Waters Xbridge Prep OBD C18 column (150×40 mm, 10 μm); flow rate: 60 mL/min; gradient: 30% – 60% B over 8 min; mobile phase A: H₂O (10mM NH₄HCO₃), mobile phase B: acetonitrile). (7-Chloro-1H-benzo[d]imidazol-2-yl)(5-(2-fluoroethyl)-7,8-dihydro-1,6-naphthyridin-6(5H)-yl)methanone was obtained. LC-MS: 359.1 [M+H]⁺. ¹H NMR (400 MHz, CDCl₃) δ 10.81 – 10.31 (m, 1H), 8.60 – 8.41 (m, 1H), 7.85 – 7.28 (m, 6H), 6.54 – 6.02 (m, 1H), 5.17 – 4.35 (m, 3H), 3.92 – 3.15 (m, 3H), 2.67 – 2.21 (m, 2H).

Example 190: (7-Chloro-1H-benzo[d]imidazol-2-yl)(5-(2-hydroxyethyl)-7,8-dihydro-1,6-naphthyridin-6(5H)-yl)methanone

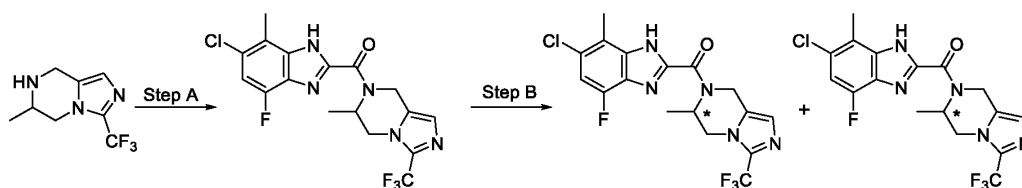


[00709] Step A: To a solution of tert-butyl 5-(2-hydroxyethyl)-7,8-dihydro-5H-1,6-naphthyridine-6-carboxylate (30.0 mg, 0.108 mmol) in EtOAc (1.00 mL) was added HCl/EtOAc (4 M, 5.00 mL). The resulting mixture was stirred at 20 °C for 0.5 h. The mixture was concentrated under reduced pressure to give 2-(5,6,7,8-tetrahydro-1,6-naphthyridin-5-yl)ethan-1-ol. LC-MS: 179.3 [M+H]⁺.

[00710] Step B: A mixture of 7-chloro-1H-benzimidazole-2-carboxylic acid (18.3 mg, 0.093 mmol), 2-(5,6,7,8-tetrahydro-1,6-naphthyridin-5-yl)ethanol (20.0 mg, 0.093 mmol), HATU (35.4 mg, 0.093 mmol) and DIEA (36.1 mg, 0.279 mmol) in DMF (0.50 mL) was stirred at 20 °C for 1 h. The reaction mixture was poured into H₂O (2.00 mL) and extracted with EtOAc (3.00 mL x 3). The combined organic layers were dried over Na₂SO₄, filtered, and concentrated under vacuum to give a residue which was purified by preparative HPLC (Phenomenex luna C18 column (100×40 mm, 5 μm); flow rate: 60 mL/min; gradient: 1% – 25% B over 8 min; mobile phase A: 0.04% aqueous HCl, mobile phase B: acetonitrile). (7-Chloro-1H-benzo[d]imidazol-2-yl)(5-(2-hydroxyethyl)-7,8-dihydro-1,6-naphthyridin-6(5H)-yl)methanone was obtained. LC-MS: 357.1 [M+H]⁺. ¹H NMR (400 MHz, DMSO-*d*₆) δ 8.80 – 8.25 (m, 2H), 7.95 – 7.68 (m, 1H), 7.62 – 7.49 (m, 1H), 7.41 – 7.32 (m, 2H), 6.81 – 5.82 (m, 1H), 5.73 – 4.66 (m, 1H), 3.83 – 3.73 (m, 4H), 2.06 – 2.04 (m, 1H), 2.29 – 1.97 (m, 2H).

Examples 191A and 191B: (R) or (S)-(6-Chloro-4-fluoro-7-methyl-1H-benzo[d]imidazol-2-yl)(6-methyl-3-(trifluoromethyl)-5,6-dihydroimidazo[1,5-a]pyrazin-7(8H)-yl)methanone

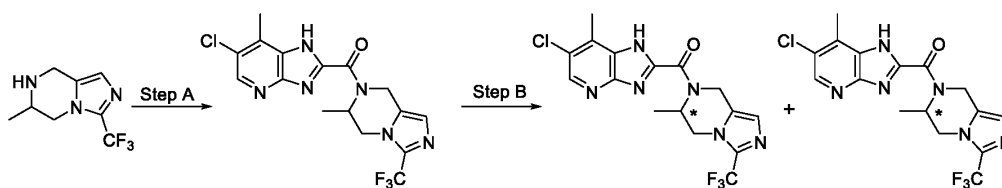
and (R) or (S)-(6-Chloro-4-fluoro-7-methyl-1H-benzo [d]imidazole-2-yl)(6-methyl-3-(trifluoromethyl)-5,6-dihydroimidazo[1,5-a]pyrazin-7(8H)-yl)methanone



[00711] Step A: To a solution of 6-chloro-4-fluoro-7-methyl-1H-benzo[d]imidazole-2-carboxylic acid (111 mg, 0.487 mmol) in DMF (2.00 mL) was added DIEA (126 mg, 0.975 mmol), 6-methyl-3-(trifluoromethyl)-5,6,7,8-tetrahydroimidazo[1,5-a]pyrazine (100 mg, 0.487 mmol) and HATU (92.7 mg, 0.244 mmol). The mixture was stirred at 25 °C for 1 h. The reaction mixture was poured into H₂O (5.00 mL) and extracted with EtOAc (5.00 mL x 3). The combined organic layers were washed with brine (3.00 mL x 3), dried over Na₂SO₄, filtered, and concentrated under vacuum to give a residue which was purified by preparative TLC (Petroleum ether: EtOAc = 1:1, R_f = 0.67). (6-Chloro-4-fluoro-7-methyl-1H-benzo[d]imidazol-2-yl)(6-methyl-3-(trifluoromethyl)-5,6-dihydroimidazo[1,5-a]pyrazin-7(8H)-yl)methanone was obtained. LC-MS: 416.2 [M+H]⁺.

[00712] Step B: (6-Chloro-4-fluoro-7-methyl-1H-benzo[d]imidazol-2-yl)(6-methyl-3-(trifluoromethyl)-5,6-dihydroimidazo[1,5-a]pyrazin-7(8H)-yl)methanone (95.0 mg, 0.228 mmol) was further separated by chiral SFC separation (DAICEL CHIRALCEL OD (250 × 30 mm, 10 μm); flow rate: 30 mL/min; gradient: 40% B over 14 min; mobile phase A: heptane, mobile phase B: CO₂ – EtOH (0.1% NH₃H₂O)). Enantiomer A: (R) or (S)-(6-chloro-4-fluoro-7-methyl-1H-benzo[d]imidazol-2-yl)(6-methyl-3-(trifluoromethyl)-5,6-dihydroimidazo[1,5-a]pyrazin-7(8H)-yl)methanone was obtained. LC-MS: 416.1 [M+H]⁺. ¹H NMR (400 MHz, CDCl₃) δ 10.98 – 10.26 (m, 1H), 7.19 – 7.08 (m, 2H), 7.07 – 6.62 (m, 1H), 5.63 – 4.55 (m, 2H), 4.49 – 4.19 (m, 2H), 2.76 – 2.45 (m, 3H), 1.43 – 1.33 (m, 3H). Enantiomer B: (R) or (S)-6-chloro-4-fluoro-7-methyl-1H-benzo[d]imidazol-2-yl)(6-methyl-3-(trifluoromethyl)-5,6-dihydroimidazo[1,5-a]pyrazin-7(8H)-yl)methanone was obtained. LC-MS: 416.1 [M+H]⁺. ¹H NMR (400 MHz, CDCl₃) δ 11.14 – 10.23 (m, 1H), 7.21 – 7.06 (m, 2H), 7.05 – 6.59 (m, 1H), 5.56 – 4.58 (m, 2H), 4.45 – 4.19 (m, 2H), 2.79 – 2.38 (m, 3H), 1.44 – 1.33 (m, 3H). The absolute stereochemistry for Enantiomer A and Enantiomer B was not determined.

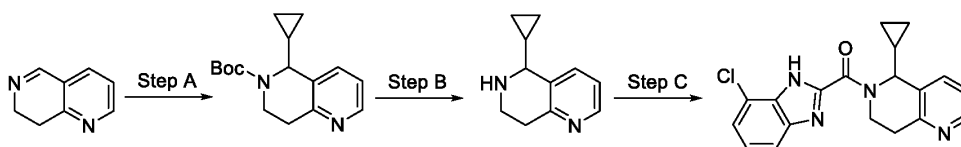
Examples 192A and 192B: (R) or (S)-(6-Chloro-7-methyl-1H-imidazo[4,5-b]pyridin-2-yl)(6-methyl-3-(trifluoromethyl)-5,6-dihydroimidazo[1,5-a]pyrazin-7(8H)-yl)methanone and (R) or (S)-(6-Chloro-7-methyl-1H-imidazo[4,5-b]pyridin-2-yl)(6-methyl-3-(trifluoromethyl)-5,6-dihydroimidazo[1,5-a]pyrazin-7(8H)-yl)methanone



[00713] Step A: To a solution of 6-methyl-3-(trifluoromethyl)-5,6,7,8-tetrahydroimidazo[1,5-a]pyrazine (100 mg, 0.487 mmol) and 6-chloro-7-methyl-1H-imidazo[4,5-b]pyridine-2-carboxylic acid (103 mg, 0.487 mmol) in DMF (2.00 mL) was added DIEA (189 mg, 1.46 mmol) and HATU (185 mg, 0.487 mmol). The mixture was stirred at 25 °C for 1 h. The mixture was poured into water (2.00 mL) and extracted with EtOAc (3.00 mL x 3). The combined organic layers were dried over Na₂SO₄, filtered, and concentrated under vacuum to give a residue which was purified by flash silica gel chromatography using a gradient of EtOAc/petroleum ether from 0/1 to 1/3. (6-Chloro-7-methyl-1H-imidazo[4,5-b]pyridin-2-yl)(6-methyl-3-(trifluoromethyl)-5,6-dihydroimidazo[1,5-a]pyrazin-7(8H)-yl)methanone was obtained. LC-MS: 399.2 [M+H]⁺.

[00714] Step B: (6-Chloro-7-methyl-1H-imidazo[4,5-b]pyridin-2-yl)(6-methyl-3-(trifluoromethyl)-5,6-dihydroimidazo[1,5-a]pyrazin-7(8H)-yl)methanone (75.0 mg, 0.188 mmol) was further separation((Phenomenex-Cellulose-2(250 × 30 mm, 10 μm); flow rate: 70 mL/min; gradient: 25 – 25% B over 11 min; mobile phase A: CO₂, mobile phase B: MeOH(0.1%NH₃H₂O)). Enantiomer A: 6-Chloro-7-methyl-1H-imidazo[4,5-b]pyridin-2-yl)(6-methyl-3-(trifluoromethyl)-5,6-dihydroimidazo[1,5-a]pyrazin-7(8H)-yl)methanone was obtained. LC-MS: 399.1 [M+H]⁺. ¹H NMR (400 MHz, CDCl₃) δ 8.58 (s, 1H), 7.10 (s, 1H), 7.04 – 6.69 (m, 1H), 5.52 – 5.16 (m, 1H), 4.75 – 4.19 (m, 3H), 2.75 (br d, *J* = 8.1 Hz, 3H), 1.41 (br d, *J* = 6.6 Hz, 3H). Enantiomer B: (6-Chloro-7-methyl-1H-imidazo[4,5-b]pyridin-2-yl)(6-methyl-3-(trifluoromethyl)-5,6-dihydroimidazo[1,5-a]pyrazin-7(8H)-yl) was obtained. LC-MS: 399.1 [M+H]⁺. ¹H NMR (400 MHz, CDCl₃) δ 8.58 (s, 1H), 7.10 (s, 1H), 7.03 – 6.66 (m, 1H), 5.48 – 5.16 (m, 1H), 4.87 – 4.16 (m, 3H), 2.75 (br d, *J* = 10.8 Hz, 3H), 1.41 (br d, *J* = 6.5 Hz, 3H). The absolute stereochemistry for Enantiomer A and Enantiomer B was not determined.

Example 193: (7-Chloro-1H-benzo[d]imidazol-2-yl)(5-cyclopropyl-7,8-dihydro-1,6-naphthyridin-6(5H)-yl)methanone

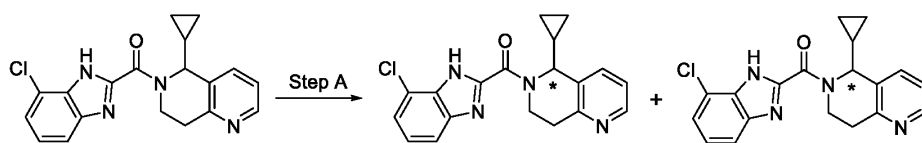


[00715] Step A: To a solution of 7,8-dihydro-1,6-naphthyridine (200 mg, 1.51 mmol) in THF (5.00 mL) was added bromo(cyclopropyl)magnesium (1M, 7.57 mL) at 0 °C under N₂, then the mixture was stirred at 0 °C to 25 °C for 1 h under N₂ atmosphere. Boc₂O (495 mg, 2.27 mmol) was added to the mixture, the resulting mixture was stirred at 25 °C for 1 h. The reaction solution was poured into H₂O (10.0 mL) and then diluted with EtOAc (10.0 mL). Then another batch of Boc₂O (400 mg) was added, the mixture was stirred at 25 °C for 12 h. Then the reaction solution was poured into H₂O (5.00 mL) and extracted with EtOAc (5.00 mL x 3). The combined organic layers were washed with brine (10.0 mL), dried over Na₂SO₄, filtered and concentrated under reduced pressure to give a residue which was purified by flash silica gel chromatography using a gradient of EtOAc/petroleum ether from 1/3 to 1/2. tert-Butyl 5-cyclopropyl-7,8-dihydro-1,6-naphthyridine-6(5H)-carboxylate was obtained. LC-MS: 275.3 [M+H]⁺. ¹H NMR (400 MHz, CDCl₃) δ 8.47 (d, *J* = 4.8 Hz, 1H), 7.83 – 7.65 (m, 1H), 7.26 – 7.19 (m, 1H), 4.73 – 4.25 (m, 2H), 3.53 – 2.89 (m, 3H), 1.49 (s, 9H), 0.82 – 0.47 (m, 5H).

[00716] Step B: A mixture of tert-butyl 5-cyclopropyl-7,8-dihydro-1,6-naphthyridine-6(5H)-carboxylate (100 mg, 0.364 mmol) in HCl/EtOAc (4M, 2.00 mL) was stirred at 25 °C for 20 min. The reaction mixture was concentrated under vacuum to give 5-cyclopropyl-5,6,7,8-tetrahydro-1,6-naphthyridine. LC-MS: 175.3 [M+H]⁺.

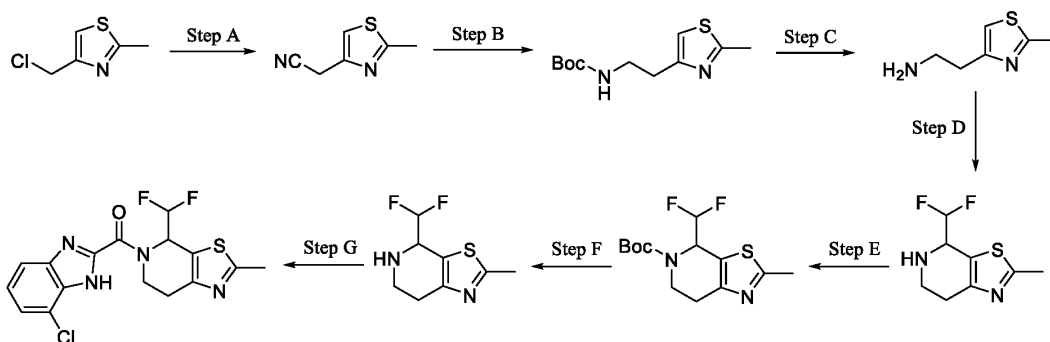
[00717] Step C: To a solution of 5-cyclopropyl-5,6,7,8-tetrahydro-1,6-naphthyridine (60.0 mg, 0.344 mmol) in DMF (1.00 mL) was added 7-chloro-1H-benzimidazole-2-carboxylic acid (67.7 mg, 0.344 mmol), DIEA (89.0 mg, 0.689 mmol) and HATU (65.5 mg, 0.172 mmol). The reaction mixture was poured into H₂O (2.00 mL) and extracted with EtOAc (1.00 mL x 3). The combined organic layers were dried over Na₂SO₄, filtered, and concentrated under vacuum to give a residue which was purified by prep-HPLC (Waters Xbridge Prep OBD C18 column (150 × 40 mm, 10 μm); flow rate: 25 mL/min; gradient: 35% – 65% B over 8 min; mobile phase A: 10 mM NH₄HCO₃, mobile phase B: acetonitrile). (7-Chloro-1H-benzo[d]imidazol-2-yl)(5-cyclopropyl-7,8-dihydro-1,6-naphthyridin-6(5H)-yl)methanone was obtained. LC-MS: 353.1 [M+H]⁺. ¹H NMR (400 MHz, CDCl₃) δ 10.70 – 10.31 (m, 1H), 8.51 (t, *J* = 3.9 Hz, 1H), 7.92 – 7.41 (m, 2H), 7.40 – 7.28 (m, 3H), 7.08 – 6.31 (m, 1H), 5.34 – 4.98 (m, 1H), 4.09 – 3.53 (m, 1H), 3.48 – 3.24 (m, 2H), 1.43 – 1.37 (m, 1H), 1.15 – 0.92 (m, 1H), 0.88 – 0.79 (m, 2H), 0.65 – 0.50 (m, 1H).

Example 193A and 193B: (R) or (S)-(7-Chloro-1H-benzo[d]imidazol-2-yl)(5-cyclopropyl-7,8-dihydro-1,6-naphthyridin-6(5H)-yl)methanone and (R) or (S)-(7-Chloro-1H-benzo[d]imidazol-2-yl)(5-cyclopropyl-7,8-dihydro-1,6-naphthyridin-6(5H)-yl)methanone



[00718] Step A: (7-Chloro-1H-benzo[d]imidazol-2-yl)(5-cyclopropyl-7,8-dihydro-1,6-naphthyridin-6(5H)-yl)methanone (30.0 mg, 0.085 mmol) was further separated by SFC separation ChiralPak IH (250 × 30 mm, 10 μm); flow rate: 30 mL/min; gradient: 40% B over 14 min; mobile phase A: heptane, mobile phase B: CO₂ – EtOH (0.1% NH₃H₂O). Two enantiomers were separated. Enantiomer A: LC-MS: 353.1 [M+H]⁺; ¹H NMR (400 MHz, CDCl₃) δ 10.56 – 10.26 (m, 1H), 8.60 – 8.48 (m, 1H), 8.01 – 7.77 (m, 1H), 7.74 – 7.42 (m, 1H), 7.41 – 7.29 (m, 3H), 7.14 – 6.37 (m, 1H), 5.45 – 4.95 (m, 1H), 4.04 – 3.56 (m, 1H), 3.53 – 3.17 (m, 2H), 1.43 – 1.35 (m, 1H), 1.21 – 0.93 (m, 1H), 0.85 (br d, *J* = 4.9 Hz, 2H), 0.64 – 0.52 (m, 1H). Enantiomer B: LC-MS: 353.1 [M+H]⁺; ¹H NMR (400 MHz, CDCl₃) δ 10.92 – 10.29 (m, 1H), 8.56 – 8.41 (m, 1H), 7.92 – 7.75 (m, 1H), 7.72 – 7.40 (m, 1H), 7.40 – 7.28 (m, 3H), 7.08 – 6.28 (m, 1H), 5.40 – 4.96 (m, 1H), 4.14 – 3.53 (m, 1H), 3.49 – 3.23 (m, 2H), 1.49 – 1.26 (m, 1H), 1.17 – 0.92 (m, 1H), 0.83 (br d, *J* = 5.4 Hz, 2H), 0.65 – 0.44 (m, 1H). The absolute stereochemistry for Enantiomer A and Enantiomer B was not determined.

Example 194: (7-Chloro-1H-benzo[d]imidazol-2-yl)(4-(difluoromethyl)-2-methyl-6,7-dihydrothiazolo[5,4-c]pyridin-5(4H)-yl)methanone



[00719] Step A: To a solution of 4-(chloromethyl)-2-methylthiazole (5.00 g, 27.2 mmol, HCl) in DMSO (100 mL) was added NaCN (3.99 g, 81.5 mmol). The resulting mixture was stirred at 20 °C for 16 h. The reaction mixture was poured into H₂O (100 mL) and extracted with EtOAc (100 mL × 4). The combined organic layers were dried over Na₂SO₄, filtered, and concentrated under vacuum to give a residue which was purified by flash chromatography on silica gel using a gradient of EtOAc/petroleum ether from 0/100 to 2/25 to give 2-(2-methylthiazol-4-yl)acetonitrile. LC-MS: 139.2 [M+H]⁺. ¹H NMR (400 MHz, CDCl₃) δ 7.13 (s, 1H), 3.85 (d, *J* = 0.8 Hz, 2H), 2.71 (s, 3H).

[00720] Step B: To a solution of 2-(2-methylthiazol-4-yl)acetonitrile (2.00 g, 11.5 mmol) and Boc_2O (2.75 g, 12.6 mmol, 2.89 mL) in MeOH (40.0 mL) was added Raney Ni (672 mg, 11.5 mmol). The mixture was stirred at 20 °C for 5 h under H_2 (15Psi). The suspension was filtered through a pad of Celite and the filtrate was concentrated under vacuum. The residue was purified by flash chromatography on silica gel using a gradient of EtOAc/petroleum ether from 0/100 to 9/50 to give tert-butyl (2-(2-methylthiazol-4-yl)ethyl)carbamate. LC-MS: 243.2 $[\text{M}+\text{H}]^+$.

[00721] Step C: To a solution of tert-butyl (2-(2-methylthiazol-4-yl)ethyl)carbamate (2.00 g, 8.25 mmol) in EtOAc (10.0 mL) was added HCl/EtOAc (4M, 10.0 mL). The mixture was stirred at 20 °C for 1 h. The mixture was concentrated under vacuum to give 2-(2-methylthiazol-4-yl)ethan-1-amine. LC-MS: 143.2 $[\text{M}+\text{H}]^+$.

[00722] Step D: A mixture of 2-(2-methylthiazol-4-yl)ethan-1-amine (0.105 g, 0.738 mmol) and 1-ethoxy-2,2-difluoro-ethanol (140 mg, 1.11 mmol) in EtOH (2.00 mL) was stirred at 90 °C for 48 h. The mixture was concentrated under vacuum to give a crude 4-(difluoromethyl)-2-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridine. LC-MS: 205.2 $[\text{M}+\text{H}]^+$.

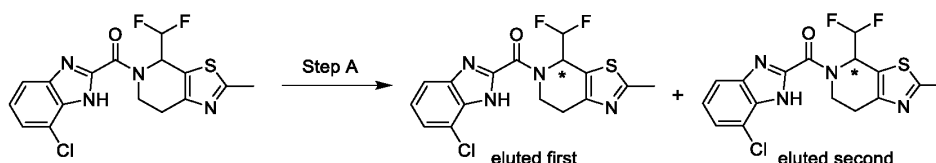
[00723] Step E: To a solution of 4-(difluoromethyl)-2-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridine (0.100 g, 0.490 mmol) in DCM (2.00 mL) was added Boc_2O (214 mg, 0.979 mmol, 225 μL) and TEA (49.5 mg, 0.490 mmol, 68.2 μL). The mixture was stirred at 20 °C for 1 h. The reaction mixture was concentrated under vacuum. The residue was purified by preparative TLC (EtOAc/petroleum ether = 1:2, R_f = 0.5) to give tert-butyl 4-(difluoromethyl)-2-methyl-6,7-dihydrothiazolo[5,4-c]pyridine-5(4H)-carboxylate. LC-MS: 305.2 $[\text{M}+\text{H}]^+$.

[00724] Step F: To a solution of tert-butyl 4-(difluoromethyl)-2-methyl-6,7-dihydrothiazolo[5,4-c]pyridine-5(4H)-carboxylate (0.040 g, 0.131 mmol) in EtOAc (1.00 mL) was added HCl/EtOAc (4M, 1.00 mL). The mixture was stirred at 20 °C for 1 h. The mixture was concentrated under vacuum to give 4-(difluoromethyl)-2-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridine. LC-MS: 205.2 $[\text{M}+\text{H}]^+$.

[00725] Step G: To a solution of 4-(difluoromethyl)-2-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridine (35.0 mg, 0.145 mmol, HCl salt), 7-chloro-1H-benzimidazole-2-carboxylic acid (28.6 mg, 0.145 mmol) in DMF (1.00 mL) was added DIEA (37.6 mg, 0.291 mmol, 50.7 μL) and HATU (27.6 mg, 0.727 mmol). The mixture was stirred at 20 °C for 1 h. The reaction mixture was purified directly by preparative HPLC (Waters Xbridge Prep OBD C18 column (150 $\times$ 40 mm, 10 μm); flow rate: 60 mL/min; gradient: 30% – 60% B over 8 min; mobile phase A: 10mM aqueous NH_4HCO_3 , mobile phase B: acetonitrile) to give (7-chloro-1H-benzo[d]imidazol-2-yl)(4-(difluoromethyl)-2-methyl-6,7-dihydrothiazolo[5,4-c]pyridin-5(4H)-yl)methanone. LC-MS: 383.1 $[\text{M}+\text{H}]^+$. ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ 13.62 (br s, 1H), 7.66 - 7.47 (m, 1H), 7.45

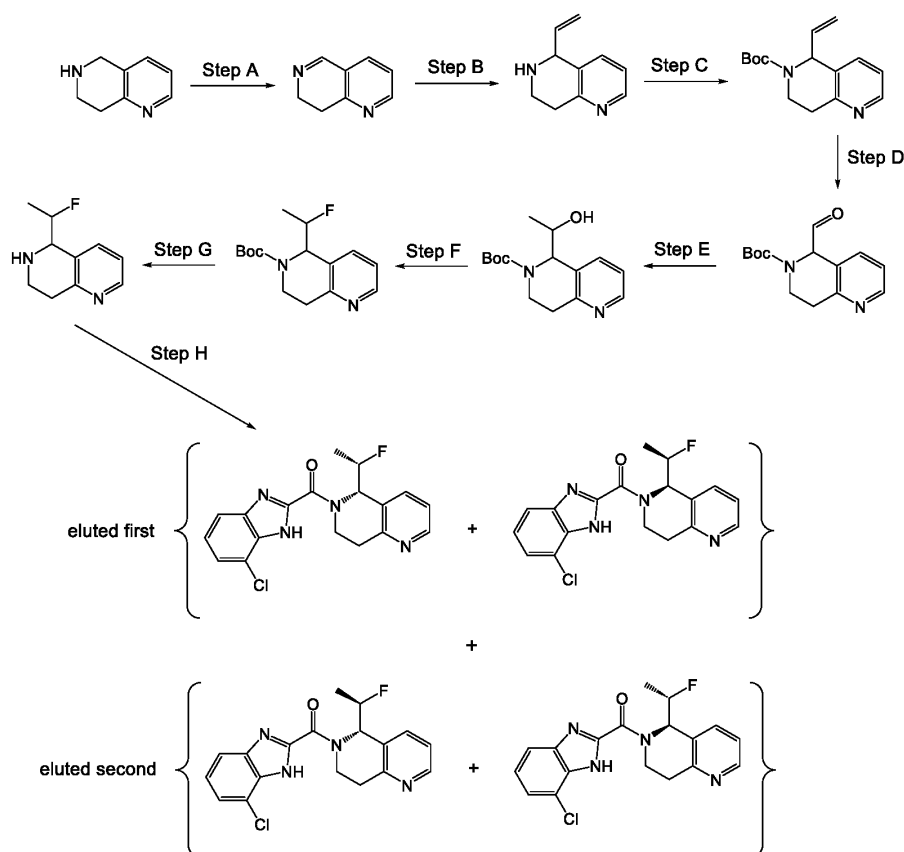
- 7.27 (m, 2H), 7.25 - 6.05 (m, 1H), 5.95 (br s, 1H), 4.98 - 3.61 (m, 1H), 3.24 (br s, 1H), 3.05 - 2.78 (m, 2H), 2.72 - 2.60 (m, 3H).

Examples 194A and 194B: (R) or (S)-(7-Chloro-1H-benzo[d]imidazol-2-yl)(4-(difluoromethyl)-2-methyl-6,7-dihydrothiazolo[5,4-c]pyridin-5(4H)-yl)methanone and (R) or (S)-(7-Chloro-1H-benzo[d]imidazol-2-yl)(4-(difluoromethyl)-2-methyl-6,7-dihydrothiazolo[5,4-c]pyridin-5(4H)-yl)methanone



[00726] Step A: (7-Chloro-1H-benzo[d]imidazol-2-yl)(4-(difluoromethyl)-2-methyl-6,7-dihydrothiazolo[5,4-c]pyridin-5(4H)-yl)methanone (20 mg) was further separated by SFC separation((DAICEL CHIRALPAK IG (250 × 30 mm, 10 μm); flow rate: 70 mL/min; gradient: 50% B over 4 min; mobile phase A: CO₂, mobile phase B: EtOH(0.1%NH₃H₂O)). First eluted compound: LC-MS: 383.0 [M+H]⁺. ¹H NMR (400 MHz, DMSO-d₆) δ 13.62 (br s, 1H), 7.66 - 7.47 (m, 1H), 7.45 - 7.27 (m, 2H), 7.25 - 6.05 (m, 1H), 5.95 (br s, 1H), 4.98 - 3.61 (m, 1H), 3.24 (br s, 1H), 3.05 - 2.78 (m, 2H), 2.72 - 2.60 (m, 3H). Second eluted compound: LC-MS: 383.0 [M+H]⁺. ¹H NMR (400 MHz, DMSO-d₆) δ 13.62 (br s, 1H), 7.66 - 7.47 (m, 1H), 7.45 - 7.27 (m, 2H), 7.25 - 6.05 (m, 1H), 5.95 (br s, 1H), 4.98 - 3.61 (m, 1H), 3.24 (br s, 1H), 3.05 - 2.78 (m, 2H), 2.72 - 2.60 (m, 3H). The absolute stereochemistry for the first and second eluted compounds was not determined.

Examples 195A and 195B: (7-Chloro-1H-benzo[d]imidazol-2-yl)((S)-5-((S)-1-fluoroethyl)-7,8-dihydro-1,6-naphthyridin-6(5H)-yl)methanone ((S),(S)/(R),(R) enantiomeric pair or (R),(S)/(S),(R) enantiomeric pair) and (7-Chloro-1H-benzo[d]imidazol-2-yl)(-5-(-1-fluoroethyl)-7,8-dihydro-1,6-naphthyridin-6(5H)-yl)methanone ((S),(S)/(R),(R) enantiomeric pair or (R),(S)/(S),(R) enantiomeric pair)



[00727] Step A: To a solution of 5,6,7,8-tetrahydro-1,6-naphthyridine (3.00 g, 22.4 mmol) in DCM (450 mL) and DMSO (4.5 mL) was added MnO_2 (35.8 g, 412 mmol). The mixture was stirred at 20 °C for 12 h. The reaction mixture was filtered through Celite pad, then the filtrate was concentrated in vacuum to give 7,8-dihydro-1,6-naphthyridine. LC-MS: 133.1 $[\text{M}+\text{H}]^+$. ^1H NMR (400 MHz, CDCl_3) δ 8.62 – 8.49 (m, 1H), 8.37 (br s, 1H), 7.58 (d, $J = 7.5$ Hz, 1H), 7.29 (s, 1H), 4.04 – 3.87 (m, 2H), 2.98 (t, $J = 7.9$ Hz, 2H).

[00728] Step B: To a solution of 7,8-dihydro-1,6-naphthyridine (2.00 g, 15.1 mmol) in THF (200 mL) was added bromo(vinyl)magnesium (1 M, 30.2 mL). The mixture was stirred at -70 °C for 1 h under N_2 . Then the mixture was stirred at 20 °C for 12 h. The reaction mixture was poured into H_2O (200 mL) and extracted with EtOAc (200 mL x 3). The combined organic layers were dried over Na_2SO_4 , filtered and concentrated under reduced pressure to give 5-vinyl-5,6,7,8-tetrahydro-1,6-naphthyridine. LC-MS: 161.3 $[\text{M}+\text{H}]^+$.

[00729] Step C: To a solution of 5-vinyl-5,6,7,8-tetrahydro-1,6-naphthyridine (2.00 g, 12.5 mmol) in MeOH (20.0 mL) and H_2O (10.0 mL) was added K_2CO_3 (3.45 g, 25.0 mmol) and Boc_2O (4.09 g, 18.7 mmol). The mixture was stirred at 20 °C for 12 h. The reaction mixture was poured into H_2O (50.0 mL) and extracted with EtOAc (50.0 mL x 3). The combined organic

layers were dried over Na_2SO_4 , filtered and concentrated under reduced pressure. The residue was purified by flash silica gel chromatography using a gradient of EtOAc/petroleum ether from 0/1 to 1/1 to give tert-butyl 5-vinyl-7,8-dihydro-1,6-naphthyridine-6(5H)-carboxylate. LC-MS: 261.2 $[\text{M}+\text{H}]^+$.

[00730] Step D: A solution of tert-butyl 5-vinyl-7,8-dihydro-5H-1,6-naphthyridine-6-carboxylate (300 mg, 1.15 mmol) in DCM (15.0 mL) was bubbled with O_3 at -78°C until the blue color persisted (30 minutes). The excess of ozone was removed by bubbling through oxygen gas for 10 minutes. Then, Me_2S (358 mg, 5.76 mmol) was added and the mixture was allowed to warm to 0°C . The reaction mixture was concentrated under reduced pressure to give tert-butyl 5-formyl-7,8-dihydro-1,6-naphthyridine-6(5H)-carboxylate.

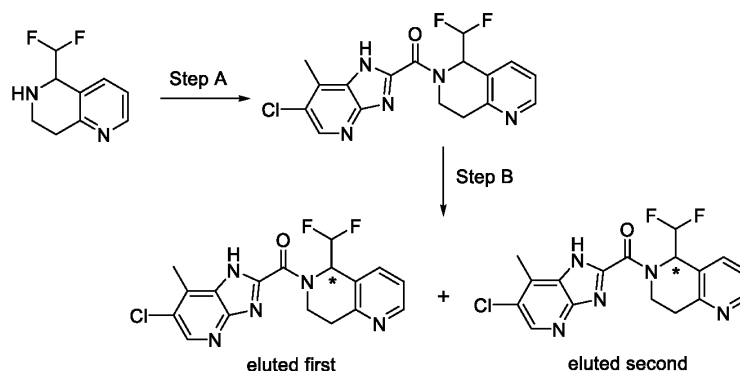
[00731] Step E: To a solution of tert-butyl 5-formyl-7,8-dihydro-5H-1,6-naphthyridine-6-carboxylate (300 mg, 1.14 mmol) in THF (20.0 mL) was added MeMgBr (3M, 762 μL). The mixture was stirred at 0°C under N_2 . Then the resulting mixture was allowed to warm to 25°C slowly under nitrogen and stirred for 12 h. The reaction mixture was poured into H_2O (10.0 mL) and extracted with DCM (10.0 mL x 4). The combined organic layers were dried over Na_2SO_4 , filtered, and concentrated under vacuum. The residue was purified by flash silica gel chromatography using a gradient of EtOAc/petroleum ether from 0/1 to 1/1 to give tert-butyl 5-(1-hydroxyethyl)-7,8-dihydro-5H-1,6-naphthyridine-6-carboxylate. LC-MS: 279.3 $[\text{M}+\text{H}]^+$. ^1H NMR (400 MHz, CDCl_3) δ 8.49 (br d, $J = 3.6$ Hz, 1H), 7.92 – 7.65 (m, 1H), 7.25 – 7.13 (m, 1H), 5.30 – 4.81 (m, 1H), 4.39 – 3.97 (m, 2H), 3.84 – 2.88 (m, 4H), 1.53 – 1.49 (m, 9H), 1.30 – 1.23 (m, 3H).

[00732] Step F: To a solution of tert-butyl 5-(1-hydroxyethyl)-7,8-dihydro-5H-1,6-naphthyridine-6-carboxylate (40.0 mg, 0.144 mmol) in DCM (5.00 mL) was added DAST (92.7 mg, 0.575 mmol) under argon at 0°C . The mixture was stirred at 0°C for 1 h. The reaction mixture was poured into saturated NaHCO_3 (10.0 mL) aqueous and extracted with EtOAc (10.0 mL x 3). The combined organic layers were dried over Na_2SO_4 , filtered and concentrated under reduced pressure. The residue was purified by preparative TLC (pure EtOAc, $R_f = 0.78$) to give tert-butyl 5-(1-fluoroethyl)-7,8-dihydro-5H-1,6-naphthyridine-6-carboxylate. LC-MS: 281.2 $[\text{M}+\text{H}]^+$.

[00733] Step G: To a solution of tert-butyl 5-(1-fluoroethyl)-7,8-dihydro-5H-1,6-naphthyridine-6-carboxylate (20.0 mg, 0.07134 mmol) in EtOAc (0.50 mL) was added HCl/EtOAc (2M, 4.00 mL). The mixture was stirred at 20°C for 1 h. The mixture was concentrated under reduced pressure to give 5-(1-fluoroethyl)-5,6,7,8-tetrahydro-1,6-naphthyridine. LC-MS: 181.3 $[\text{M}+\text{H}]^+$.

[00734] Step H: To a solution of 5-(1-fluoroethyl)-5,6,7,8-tetrahydro-1,6-naphthyridine (15.0 mg, 0.069.23 mmol), 7-chloro-1H-benzimidazole-2-carboxylic acid (13.6 mg, 0.069 mmol) in DCM (3.00 mL) was added BOP-Cl (26.4 mg, 0.104 mmol) and TEA (21.0 mg, 0.208 mmol). The mixture was stirred at 20 °C for 1 h. The reaction mixture was poured into H₂O (2.00 mL) and extracted with EtOAc (3.00 mL x 3). The combined organic layers were dried over Na₂SO₄, filtered and concentrated under reduced pressure. The residue was purified by preparative HPLC (Phenomenex Luna C18 column (100× 40 mm, 5 μm); flow rate: 25 mL/min; gradient: 10% – 30% B over 8 min; mobile phase A: 0.04% aqueous HCl, mobile phase B: acetonitrile). First eluted compound: LC-MS: 359.1 [M+H]⁺. ¹H NMR (400 MHz, DMSO-*d*₆) δ 8.40 - 8.78 (m, 2H), 7.70 – 7.90 (m, 1H), 7.48 – 7.62 (m, 1H), 7.24 – 7.46 (m, 2H), 5.92 – 6.24 (m, 1H), 5.30 – 5.87 (m, 2H), 3.78 – 3.83 (m, 1H), 3.37 – 3.49 (m, 1H), 3.17 – 3.29 (m, 1H), 1.30 – 1.62 ppm (m, 3H). Second eluted compound: LC-MS: 359.1 [M+H]⁺. ¹H NMR (400 MHz, DMSO-*d*₆) δ 8.49 – 8.94 (m, 1H), 8.11 – 8.41 (m, 1H), 7.64 – 7.85 (m, 1H), 7.49 – 7.62 (m, 1H), 7.26 – 7.44 (m, 2H), 5.53 – 6.01 (m, 1H), 5.03 – 5.50 (m, 1H), 3.90 – 3.95 (m, 1H), 3.40 – 3.46 (m, 1H), 3.16 – 3.32 (m, 2H), 1.26 – 1.72 (m, 3H). The diastereomers were separated as racemic mixtures. The assignment of the (S),(S)/(R),(R) enantiomeric pair to the first eluent and the (R),(S)/(S),(R) enantiomeric pair to the second eluent was done arbitrarily.

Examples 196A and 196B: (R) or (S)-(6-Chloro-7-methyl-1H-imidazo[4,5-b]pyridin-2-yl)(5-(difluoromethyl)-7,8-dihydro-1,6-naphthyridin-6(5H)-yl)methanone and (R) or (S)-(6-Chloro-7-methyl-1H-imidazo[4,5-b]pyridin-2-yl)(5-(difluoromethyl)-7,8-dihydro-1,6-naphthyridin-6(5H)-yl)methanone

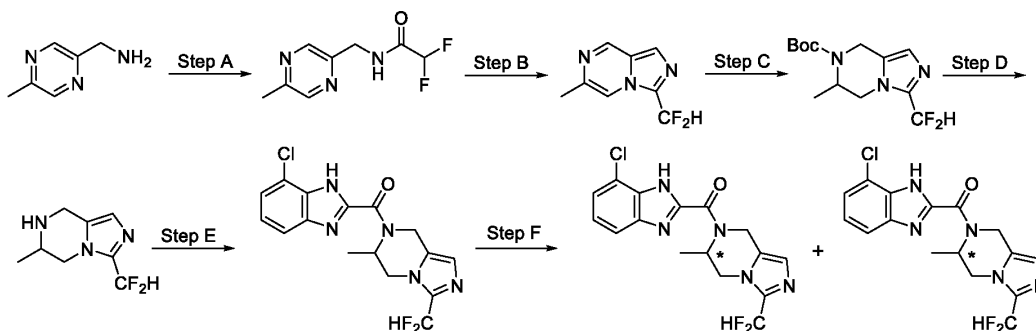


[00735] Step A: To a solution of 5-(difluoromethyl)-5,6,7,8-tetrahydro-1,6-naphthyridine (50.0 mg, 0.271 mmol), 6-chloro-7-methyl-1H-imidazo[4,5-b]pyridine-2-carboxylic acid (57.4 mg, 0.271 mmol) in DCM (10.0 mL) was added BOP-Cl (104 mg, 0.407 mmol) and TEA (82.4 mg, 0.814 mmol). The mixture was stirred at 20 °C for 1 h. The reaction mixture was added to H₂O (20.0 mL) and extracted with DCM (10.0 mL x 3). The combined organic layers were dried over

Na₂SO₄, filtered and concentrated under reduced pressure. The residue was purified by flash silica gel chromatography using a gradient of EtOAc/petroleum ether from 0/1 to 1/1 to give (6-chloro-7-methyl-1H-imidazo[4,5-b]pyridin-2-yl)(5-(difluoromethyl)-7,8-dihydro-1,6-naphthyridin-6(5H)-yl)methanone. LC-MS: 378.2 [M+H]⁺.

[00736] Step B: (6-Chloro-7-methyl-1H-imidazo[4,5-b]pyridin-2-yl)(5-(difluoromethyl)-7,8-dihydro-1,6-naphthyridin-6(5H)-yl)methanone (50.0 mg, 0.133 mmol) was further separated by SFC separation (DAICEL CHIRALCEL OD (250 × 25 mm, 10 μm); flow rate: 30 mL/min; gradient: 30% B over 14 min; mobile phase A: heptane, mobile phase B: CO₂ – EtOH (0.1% NH₃H₂O). First eluted compound: LC-MS: 378.1 [M+H]⁺. ¹H NMR (400 MHz, DMSO-*d*₆) δ 14.19 – 13.81 (m, 1H), 8.62 – 8.37 (m, 2H), 8.06 – 7.78 (m, 1H), 7.35 (td, *J* = 5.0, 7.8 Hz, 1H), 6.80 – 6.36 (m, 1H), 6.23 – 5.33 (m, 1H), 4.92 – 3.84 (m, 1H), 3.59 – 3.39 (m, 1H), 3.24 – 2.94 (m, 2H), 2.65 (d, *J* = 5.4 Hz, 3H). Second eluted compound: LC-MS: 378.1 [M+H]⁺. ¹H NMR (400 MHz, DMSO-*d*₆) δ 14.29 – 13.65 (m, 1H), 8.65 – 8.32 (m, 2H), 8.03 – 7.69 (m, 1H), 7.45 – 6.98 (m, 1H), 6.75 – 6.37 (m, 1H), 6.20 – 5.35 (m, 1H), 4.97 – 3.83 (m, 1H), 3.56 – 3.33 (m, 1H), 3.27 – 2.88 (m, 2H), 2.65 (d, *J* = 5.3 Hz, 3H). The absolute stereochemistry for the first and second eluted compounds was not determined.

Examples 197A and 197B: (R) or (S)-(7-Chloro-1H-benzo[d]imidazol-2-yl)(3-(difluoromethyl)-6-methyl-5,6-dihydroimidazo[1,5-a]pyrazin-7(8H)-yl)methanone and (R) or (S)-(7-Chloro-1H-benzo[d]imidazol-2-yl)(3-(difluoromethyl)-6-methyl-5,6-dihydroimidazo[1,5-a]pyrazin-7(8H)-yl)methanone

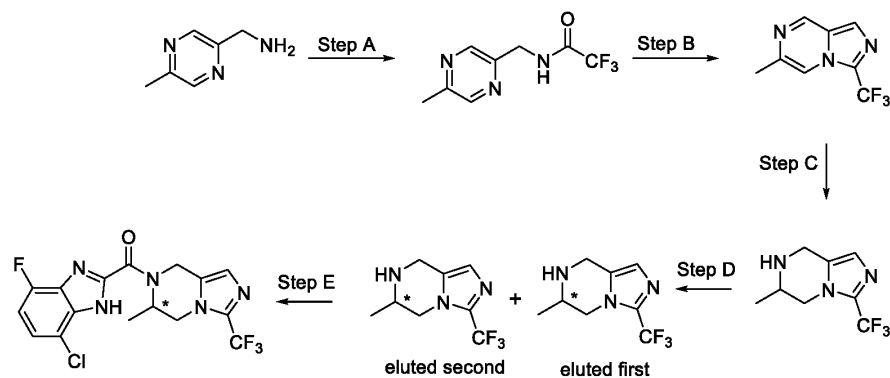


[00737] Step A, B, C, D, E: (7-Chloro-1H-benzo[d]imidazol-2-yl)(3-(difluoromethyl)-6-methyl-5,6-dihydroimidazo[1,5-a]pyrazin-7(8H)-yl)methanone was prepared from 5-methylpyrazin-2-yl)methanamine according to the procedure of Example 10, Steps C, D, E, and F. LC-MS: 366.3 [M+H]⁺.

[00738] Step F: (7-Chloro-1H-benzo[d]imidazol-2-yl)(3-(difluoromethyl)-6-methyl-5,6-dihydroimidazo[1,5-a]pyrazin-7(8H)-yl)methanone (100 mg, 0.273 mmol) was further separated

by SFC separation (DAICEL CHIRALPAK AD (250 × 30 mm, 10 μm); flow rate: 30 mL/min; gradient: 65% B over 14 min; mobile phase A: heptane, mobile phase B: CO₂ – EtOH (0.1% NH₃H₂O). First eluted compound: LC-MS: 366.1 [M+H]⁺. ¹H NMR (400 MHz, DMSO-d₆) δ 13.77 – 13.26 (m, 1H), 7.61 – 7.32 (m, 2H), 7.31 – 7.10 (m, 1H), 7.07 – 6.96 (m, 1H), 6.31 – 4.57 (m, 2H), 4.45 – 4.24 (m, 2H), 3.39 – 3.35 (m, 1H), 3.30 – 3.28 (m, 1H), 1.31 – 1.13 (m, 3H). Second eluted compound: LC-MS: 366.1 [M+H]⁺. ¹H NMR (400 MHz, DMSO-d₆) δ 13.79 – 13.25 (m, 1H), 7.58 – 7.32 (m, 2H), 7.31 – 7.10 (m, 1H), 7.08 – 6.93 (m, 1H), 6.19 – 4.63 (m, 2H), 4.43 – 4.28 (m, 2H), 3.45 – 3.35 (m, 1H), 3.31 – 3.21 (m, 1H), 1.29 – 1.12 (m, 3H). The absolute stereochemistry for the first and second eluted compounds was not determined.

Example 198: (7-Chloro-4-fluoro-1H-benzo[d]imidazol-2-yl)(6-methyl-3-(trifluoromethyl)-5,6-dihydroimidazo[1,5-a]pyrazin-7(8H)-yl)methanone



[00739] Step A: To a solution of (5-methylpyrazin-2-yl)methanamine (50.0 g, 406 mmol) in DCM (500 mL) was added TFAA (102 g, 487 mmol) under -10 °C, then the mixture was stirred at 20 °C overnight. The mixture was poured into H₂O (500 mL) and extracted with DCM (300 mL x 5). The combined organic layers were dried over Na₂SO₄, filtered, and concentrated under vacuum to give a residue, which was triturated with EtOAc : Petroleum ether=10:1 (50 ml) at 20 °C for 30 min. The mixture was filtered and the cake was dried in vacuum to give 2,2,2-trifluoro-N-((5-methylpyrazin-2-yl)methyl)acetamide (80 g, 90%). LC-MS: 220.0 [M+H]⁺. ¹H NMR (400 MHz, CDCl₃) δ 8.53 (s, 1H), 8.45 (s, 1H), 7.57 (br s, 1H), 4.67 (d, *J* = 5.0 Hz, 2H), 2.61 (s, 3H).

[00740] Step B: To a solution of 2,2,2-trifluoro-N-((5-methylpyrazin-2-yl)methyl)acetamide (80.0 g, 365 mmol) in POCl₃ (380 mL) was added P₂O₅ (51.8 g, 365 mmol). The flask was equipped with a condenser and the mixture was heated at 120 °C overnight. The reaction mixture was allowed to cool to room temperature and concentrated under vacuum to remove most of the POCl₃, then the mixture was added into 400 ml of EtOAc to give a solution, which was poured into saturated Na₂CO₃ (aq. 400 ml) at 0 °C, then the mixture was poured into H₂O (200 mL) and extracted with DCM (500 mL x 3). The combined organic layers were dried in vacuum to give a

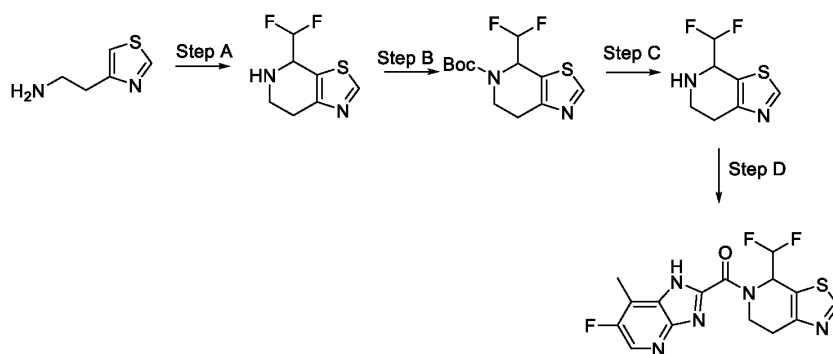
residue. The residue was adsorbed on silica to be purified by flash chromatography on silica gel using a gradient of EtOAc in heptanes (0 to 50% gradient) to give 6-methyl-3-(trifluoromethyl)imidazo[1,5-a]pyrazine (65 g, 89%). LC-MS: 202.0 [M+H]⁺. ¹H NMR (400 MHz, CDCl₃) δ 9.07 (s, 1H), 7.85 (s, 2H), 2.53 (s, 3H).

[00741] Step C: To a mixture of 6-methyl-3-(trifluoromethyl)imidazo[1,5-a]pyrazine (50.0 g, 248 mmol) in THF (150 mL) was added Pd/C (47.5 g, 10% purity). The mixture was degassed and purged with H₂ three times and stirred at 20 °C for 12 h under a H₂ atmosphere (15 psi). The mixture was filtered and the filtrate was concentrated in vacuum to give 6-methyl-3-(trifluoromethyl)-5,6,7,8-tetrahydroimidazo[1,5-a]pyrazine (43 g, 84% yield). LC-MS: 206.0 [M+H]⁺. ¹H NMR (400 MHz, DMSO-d₆) δ 6.84 (s, 1H), 4.19 - 4.01 (m, 2H), 3.83 (br d, *J* = 16.0 Hz, 1H), 3.48 (t, *J* = 11.3 Hz, 1H), 3.09 - 2.94 (m, 1H), 2.73 - 2.55 (m, 1H), 1.14 (d, *J* = 6.4 Hz, 3H).

[00742] Step D: 6-methyl-3-(trifluoromethyl)-5,6,7,8-tetrahydroimidazo[1,5-a]pyrazine (43 g, 210 mmol) was further separated by SFC separation ((DAICEL CHIRALPAK IC (250 × 50 mm, 10 μm); flow rate: 64 mL/min; gradient: 25% B over 4 min; mobile phase A: CO₂, mobile phase B: isopropanol (0.1% NH₃H₂O)). (R) or (S)-6-methyl-3-(trifluoromethyl)-5,6,7,8-tetrahydroimidazo[1,5-a]pyrazine (18.0 g, eluent first). LC-MS: 206.0 [M+H]⁺. ¹H NMR (400 MHz, DMSO-d₆) δ = 6.84 (s, 1H), 4.14 (br dd, *J* = 3.2, 11.9 Hz, 1H), 4.05 (d, *J* = 16.0 Hz, 1H), 3.83 (br d, *J* = 16.0 Hz, 1H), 3.48 (t, *J* = 11.3 Hz, 1H), 3.14 - 2.95 (m, 1H), 1.14 (d, *J* = 6.4 Hz, 4H). (R) or (S)-6-methyl-3-(trifluoromethyl)-5,6,7,8-tetrahydroimidazo[1,5-a]pyrazine (16.8 g, eluent second). LC-MS: LC-MS: 206.0 [M+H]⁺. ¹H NMR (400 MHz, DMSO-d₆) δ = 6.84 (s, 1H), 4.14 (dd, *J* = 3.6, 11.9 Hz, 1H), 4.05 (d, *J* = 16.0 Hz, 1H), 3.83 (br d, *J* = 16.0 Hz, 1H), 3.55 - 3.42 (m, 1H), 3.11 - 2.93 (m, 1H), 1.14 (d, *J* = 6.4 Hz, 4H).

[00743] Step E: The title compound was prepared from 7-chloro-4-fluoro-1H-benzimidazole-2-carboxylic acid and 6-methyl-3-(trifluoromethyl)-5,6,7,8-tetrahydroimidazo[1,5-a]pyrazine (eluted second) according to the procedure of Example 1, Step A as a single enantiomer. The absolute stereochemistry was not determined. LC-MS: 402.1 [M+H]⁺. ¹H NMR (400 MHz, CDCl₃) δ 10.64 - 10.27 (m, 1H), 7.36 - 7.29 (m, 1H), 7.14 - 7.09 (m, 1H), 7.08 - 6.61 (m, 2H), 5.52 - 4.58 (m, 2H), 4.44 - 4.21 (m, 2H), 1.39 (br t, *J* = 7.1 Hz, 3H).

Example 199: 4-(Difluoromethyl)-6,7-dihydrothiazolo[5,4-c]pyridin-5(4H)-yl)(6-fluoro-7-methyl-1H-imidazo[4,5-b]pyridin-2-yl)methanone



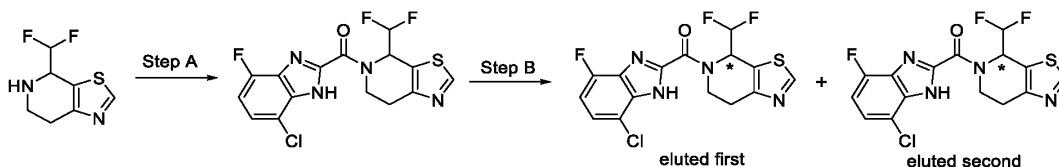
[00744] Step A: A solution of 2-thiazol-4-ylethanamine (50.0 mg, 0.304 mmol), 1-ethoxy-2,2-difluoro-ethanol (57.4 mg, 0.456 mmol) in EtOH (1.00 mL) was stirred at 90 °C for 12 h. The mixture was concentrated under vacuum to give 4-(difluoromethyl)-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridine. LC-MS: 191.0 [M+H]⁺.

[00745] Step B: To a solution of 4-(difluoromethyl)-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridine (50.0 mg, 0.263 mmol) in DCM (1.00 mL) was added Boc₂O (115 mg, 0.526 mmol) and TEA (26.6 mg, 0.263 mmol). The mixture was stirred at 20 °C for 1 h. The reaction mixture was poured into H₂O (2.00 mL) and extracted with EtOAc (3.00 mL X 3). The combined organic layers were dried over Na₂SO₄, filtered and concentrated under reduced pressure. The residue was purified by preparative TLC (SiO₂, Petroleum ether: EtOAc =5:1) to give tert-butyl 4-(difluoromethyl)-6,7-dihydrothiazolo[5,4-c]pyridine-5(4H)-carboxylate. LC-MS: 291.0 [M+H]⁺.

[00746] Step C: To a solution of tert-butyl 4-(difluoromethyl)-6,7-dihydrothiazolo[5,4-c]pyridine-5(4H)-carboxylate (35.0 mg, 0.121 mmol) in EtOAc (2.00 mL) was added HCl/EtOAc (2 M, 5.00 mL). The mixture was stirred at 20 °C for 1 h. The mixture was concentrated under vacuum at 30 °C to give 4-(difluoromethyl)-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridine. LC-MS: 191.2 [M+H]⁺.

[00747] Step D: To a solution of 4-(difluoromethyl)-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridine (58.5 mg, 0.307 mmol) in THF (2.00 mL) was added 6-fluoro-7-methyl-1H-imidazo[4,5-b]pyridine-2-carboxylic acid (60.0 mg, 307 mmol), BOP-Cl (86.1 mg, 0.338 mmol) and DIEA (119 mg, 0.922 mmol). The mixture was stirred at 20 °C for 12 h. The reaction mixture was treated with NaOH (2M aqueous) and stirred at room temperature for 30 min. The mixture was filtered and the filter cake was lyophilized to give (4-(difluoromethyl)-6,7-dihydrothiazolo[5,4-c]pyridin-5(4H)-yl)(6-fluoro-7-methyl-1H-imidazo[4,5-b]pyridin-2-yl)methanone. LC-MS: 368.1 [M+H]⁺. ¹H NMR (400 MHz, DMSO-d₆) δ 9.12 (d, *J* = 13.1 Hz, 1H), 7.96 (dd, *J* = 2.2, 9.8 Hz, 1H), 7.09 – 6.62 (m, 1H), 6.58 – 6.05 (m, 1H), 5.13 – 4.84 (m, 1H), 3.48 – 3.39 (m, 1H), 3.22 – 3.16 (m, 1H), 3.01 – 2.82 (m, 2H), 2.41 (br d, *J* = 2.1 Hz, 3H).

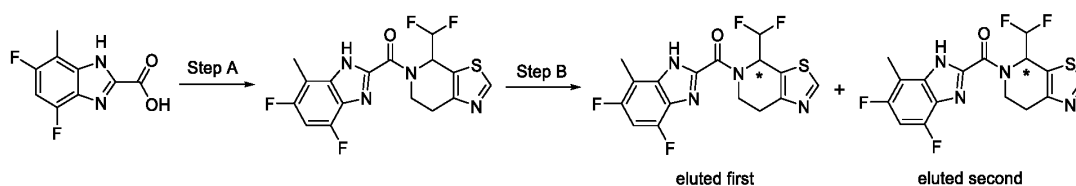
Examples 200A and 200B: (R) or (S)-(7-Chloro-4-fluoro-1H-benzo[d]imidazol-2-yl)(4-(difluoromethyl)-6,7-dihydrothiazolo[5,4-c]pyridin-5(4H)-yl)methanone and (R) or (S)-(7-Chloro-4-fluoro-1H-benzo[d]imidazol-2-yl)(4-(difluoromethyl)-6,7-dihydrothiazolo[5,4-c]pyridin-5(4H)-yl)methanone



[00748] Step A: To a solution of 4-(difluoromethyl)-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridine (100 mg, 0.441 mmol) in DCM (3.00 mL) was added 7-chloro-4-fluoro-1H-benzimidazole-2-carboxylic acid (94.7 mg, 0.441 mmol), BOP-Cl (112 mg, 0.441 mmol) and TEA (134 mg, 1.32 mmol). The mixture was stirred at 20 °C for 1 h. The reaction mixture was poured into H₂O (5.00 mL) and extracted with DCM (5.00 mL x 3). The combined organic layers were dried over Na₂SO₄, filtered, and concentrated under vacuum. The residue was purified by flash silica gel chromatography using a gradient of EtOAc/petroleum ether from 0/1 to 1/1 to give (7-chloro-4-fluoro-1H-benzo[d]imidazol-2-yl)(4-(difluoromethyl)-6,7-dihydrothiazolo[5,4-c]pyridin-5(4H)-yl)methanone. LC-MS: 387.1 [M+H]⁺.

[00749] Step B: (7-Chloro-4-fluoro-1H-benzo[d]imidazol-2-yl)(4-(difluoromethyl)-6,7-dihydrothiazolo[5,4-c]pyridin-5(4H)-yl)methanone (55.0 mg, 0.134 mmol) was further separated by SFC separation ChiralPak IH (250 × 30 mm, 10 μm); flow rate: 30 mL/min; gradient: 30% B over 14 min; mobile phase A: heptane, mobile phase B: CO₂ – IPA (0.1% NH₃H₂O). First eluted compound: LC-MS: 386.9 [M+H]⁺. ¹H NMR (400 MHz, CDCl₃) δ 10.78 – 10.40 (m, 1H), 8.86 (d, *J* = 2.1 Hz, 1H), 7.38 – 7.31 (m, 1H), 7.12 – 7.00 (m, 1H), 6.70 – 6.07 (m, 2H), 5.26 – 3.00 (m, 4H). Second eluted compound: LC-MS: 387.0 [M+H]⁺. ¹H NMR (400 MHz, CDCl₃) δ 10.79 – 10.42 (m, 1H), 8.86 (d, *J* = 2.8 Hz, 1H), 7.35 – 7.29 (m, 1H), 7.13 – 6.98 (m, 1H), 6.68 – 5.96 (m, 2H), 5.25 – 3.09 (m, 4H). The absolute stereochemistry for the first and second eluted compounds was not determined.

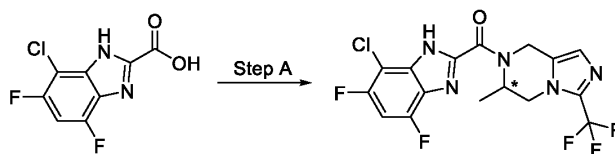
Examples 201A and 201B: (R) or (S)-(4,6-Difluoro-7-methyl-1H-benzo[d]imidazol-2-yl)(4-(difluoromethyl)-6,7-dihydrothiazolo[5,4-c]pyridin-5(4H)-yl)methanone and (R) or (S)-(4,6-Difluoro-7-methyl-1H-benzo[d]imidazol-2-yl)(4-(difluoromethyl)-6,7-dihydrothiazolo[5,4-c]pyridin-5(4H)-yl)methanone



[00750] Step A: To a solution of 4,6-difluoro-7-methyl-1H-benzimidazole-2-carboxylic acid (100 mg, 0.471 mmol) in DCM (3.00 mL) was added 4-(difluoromethyl)-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridine (89.7 mg, 0.471 mmol), TEA (95.4 mg, 0.943 mmol) and BOP-Cl (120 mg, 0.471 mmol). The mixture was stirred at 20 °C for 1 h. The reaction mixture was poured into H₂O (5.00 mL) and extracted with DCM (5.00 mL x 3). The combined organic layers were dried over Na₂SO₄, filtered, and concentrated under vacuum. The residue was purified by flash silica gel chromatography using a gradient of EtOAc/petroleum ether from 0/1 to 1/1 to give (4,6-difluoro-7-methyl-1H-benzo[d]imidazol-2-yl)(4-(difluoromethyl)-6,7-dihydrothiazolo[5,4-c]pyridin-5(4H)-yl)methanone. LC-MS: 385.1 [M+H]⁺.

[00751] Step B: (4,6-Difluoro-7-methyl-1H-benzo[d]imidazol-2-yl)(4-(difluoromethyl)-6,7-dihydrothiazolo[5,4-c]pyridin-5(4H)-yl)methanone (60.0 mg, 0.150 mmol) was further separated by SFC separation DAICEL CHIRALPAK AD (250 × 30 mm, 10 μm); flow rate: 30 mL/min; gradient: 45% B over 14 min; mobile phase A: heptane, mobile phase B: CO₂ – EtOH (0.1% NH₃H₂O). First eluted compound: LC-MS: 385.0 [M+H]⁺. ¹H NMR (400 MHz, CDCl₃) δ 10.48 – 10.17 (m, 1H), 8.86 (s, 1H), 7.54 – 7.30 (m, 1H), 7.02 – 5.01 (m, 3H), 3.86 – 3.33 (m, 1H), 3.30 – 2.99 (m, 2H), 2.60 – 2.40 (m, 3H). Second eluted compound: LC-MS: 385.0 [M+H]⁺. ¹H NMR (400 MHz, CDCl₃) δ 10.59 – 10.20 (m, 1H), 8.87 (s, 1H), 7.59 – 7.32 (m, 1H), 7.07 – 5.04 (m, 3H), 3.84 – 3.40 (m, 1H), 3.30 – 3.05 (m, 2H), 2.64 – 2.30 (m, 3H). The absolute stereochemistry for the first and second eluted compounds was not determined.

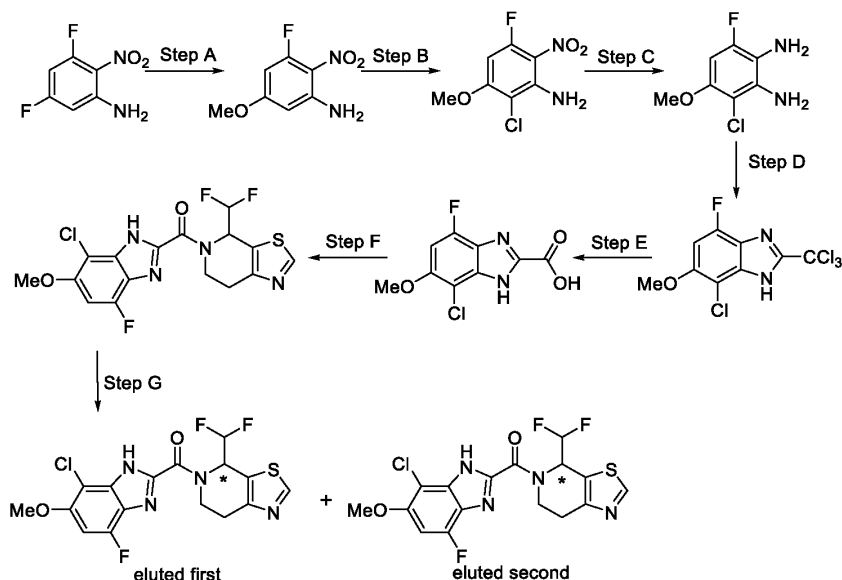
Example 202: (7-Chloro-4,6-difluoro-1H-benzo[d]imidazol-2-yl)(6-methyl-3-(trifluoromethyl)-5,6-dihydroimidazo[1,5-a]pyrazin-7(8H)-yl)methanone



[00752] Step A: A mixture of 7-chloro-4,6-difluoro-1H-benzo[d]imidazole-2-carboxylic acid (88.2 mg, 0.429 mmol), 6-methyl-3-(trifluoromethyl)-5,6,7,8-tetrahydroimidazo[1,5-a]pyrazine (eluted second, example 198) (100 mg, 0.429 mmol), HATU (164 mg, 0.429 mmol) and DIEA (167 mg, 1.29 mmol) in DMF (2.00 mL) was stirred at 20 °C for 12 h. The mixture was concentrated under vacuum at 30 °C to give a residue which was purified by preparative HPLC

(Waters Xbridge Prep OBD C18 column (150 × 40 mm, 10 μm); flow rate: 25 mL/min; gradient: 35% – 65% B over 8 min; mobile phase A: water (10 mM NH₄HCO₃), mobile phase B: acetonitrile). (7-Chloro-4,6-difluoro-1H-benzo[d]imidazol-2-yl)(6-methyl-3-(trifluoromethyl)-5,6-dihydroimidazo[1,5-a]pyrazin-7(8H)-yl)methanone was obtained as a single enantiomer. The absolute stereochemistry was not determined. LC-MS: 420.1 [M+H]⁺. ¹H NMR (400 MHz, CDCl₃) δ 7.16 – 6.97 (m, 2H), 6.96 – 6.57 (m, 1H), 5.45 – 4.64 (m, 2H), 4.43 – 4.23 (m, 2H), 3.13 – 2.48 (m, 1H), 1.47 – 1.34 (m, 3H).

Examples 203A and 203B: (R) or (S)-(7-Chloro-4-fluoro-6-methoxy-1H-benzo[d]imidazol-2-yl)(4-(difluoromethyl)-6,7-dihydrothiazolo[5,4-c]pyridin-5(4H)-yl)methanone and (R) or (S)-(7-Chloro-4-fluoro-6-methoxy-1H-benzo[d]imidazol-2-yl)(4-(difluoromethyl)-6,7-dihydrothiazolo[5,4-c]pyridin-5(4H)-yl)methanone



[00753] Step A: To a solution of 3,5-difluoro-2-nitro-aniline (2.50 g, 14.3 mmol) in THF (50.0 mL) was added a solution of NaOMe (930 mg, 17.2 mmol) in MeOH (10.0 mL) dropwise at -78 °C under a N₂ atmosphere. The mixture was stirred at 20 °C for 12 h. The reaction mixture was poured into H₂O (20.0 mL) and extracted with EtOAc (20.0 mL x 3). The combined organic layers were dried over Na₂SO₄, filtered, and concentrated under vacuum. The residue was purified by flash silica gel chromatography using a gradient of EtOAc/petroleum ether from 0/1 to 1/1 to give 3-fluoro-5-methoxy-2-nitroaniline. ¹H NMR (400 MHz, DMSO-d₆) δ 7.30 (br s, 2H), 6.33 – 6.12 (m, 2H), 3.76 (s, 3H).

[00754] Step B: To a solution of 3-fluoro-5-methoxy-2-nitro-aniline (1.60 g, 8.60 mmol) in acetonitrile (20.0 mL) was added NCS (1.15 g, 8.60 mmol). The mixture was stirred at 70 °C for

12 h. The reaction mixture was poured into H₂O (30.0 mL) and extracted with EtOAc (30.0 mL x 3). The combined organic layers were dried over Na₂SO₄, filtered, and concentrated under vacuum to give 2-chloro-5-fluoro-3-methoxy-6-nitro-aniline. LC-MS: 221.1 [M+H]⁺. ¹H NMR (400 MHz, DMSO-d₆) δ 6.97 (br s, 2H), 6.68 (br d, *J* = 14.0 Hz, 1H), 4.00 – 3.86 (m, 3H).

[00755] Step C: To a solution of 2-chloro-5-fluoro-3-methoxy-6-nitro-aniline (500 mg, 2.27 mmol) in EtOH (6.00 mL) and H₂O (2.00 mL) was added Fe (1.01 g, 18.1 mmol) and NH₄Cl (969 mg, 18.1 mmol). The mixture was stirred at 70 °C for 1 h. The reaction mixture was filtered and the filtrate was concentrated to give a residue. The residue was extracted with DCM (100 mL x 2), and the combined organic layers were washed with brine (100 mL x 3), dried over Na₂SO₄, filtered and concentrated in vacuum. The residue was purified by flash silica gel chromatography using a gradient of EtOAc/petroleum ether from 0/1 to 1/1 to give 3-chloro-6-fluoro-4-methoxybenzene-1,2-diamine. LC-MS: 191.1 [M+H]⁺. ¹H NMR (400 MHz, DMSO-d₆) δ 6.25 (d, *J* = 12.5 Hz, 1H), 5.09 (s, 2H), 4.23 (s, 2H), 3.68 (s, 3H).

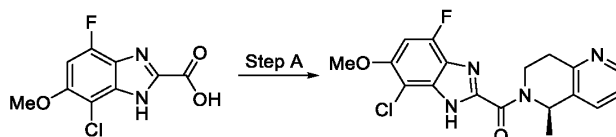
[00756] Step D: To a solution of 3-chloro-6-fluoro-4-methoxybenzene-1,2-diamine (350 mg, 1.84 mmol) in AcOH (4.00 mL) was added methyl 2,2,2-trichloroethanimidate (324 mg, 1.84 mmol). The mixture was stirred at 20 °C for 2 h. The reaction mixture was filtered, and the filter cake was washed with water (10.0 mL), and dried under reduced pressure to give 7-chloro-4-fluoro-6-methoxy-2-(trichloromethyl)-1H-benzimidazole, which was used without further purification.

[00757] Step E: A mixture of 7-chloro-4-fluoro-6-methoxy-2-(trichloromethyl)-1H-benzimidazole (500 mg, 1.57 mmol) and NaOH (2M aqueous, 4.31 mL) was stirred at 20 °C for 2 h. The reaction mixture was filtered, and the filter cake was washed with water (10.0 mL), and dried under reduced pressure to give 7-chloro-4-fluoro-6-methoxy-1H-benzimidazole-2-carboxylic acid. LC-MS: 245.0 [M+H]⁺. ¹H NMR (400 MHz, DMSO-d₆) δ 7.24 (d, *J* = 12.3 Hz, 1H), 3.91 (s, 3H).

[00758] Step F: To a solution of 7-chloro-4-fluoro-6-methoxy-1H-benzimidazole-2-carboxylic acid (84.2 mg, 0.344 mmol) and 4-(difluoromethyl)-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridine (78 mg, 0.344 mmol, HCl) in DCM (2.00 mL) was added TEA (104 mg, 1.03 mmol) and BOP-Cl (175 mg, 0.688 mmol) at 20 °C. The mixture was stirred at 20 °C for 1 h. The reaction mixture was diluted with H₂O (10.0 mL) and extracted with DCM (10.0 mL x 3). The combined organic layers were dried over Na₂SO₄, filtered and the filtrate was concentrated in vacuum. The residue was purified by preparative TLC (SiO₂, Petroleum ether/Ethyl acetate=1/1, R_f=0.2) to give 7-chloro-4-fluoro-6-methoxy-1H-benzimidazol-2-yl)-[4-(difluoromethyl)-6,7-dihydro-4H-thiazolo[5,4-c]pyridin-5-yl]methanone. LC-MS: 416.9 [M+H]⁺.

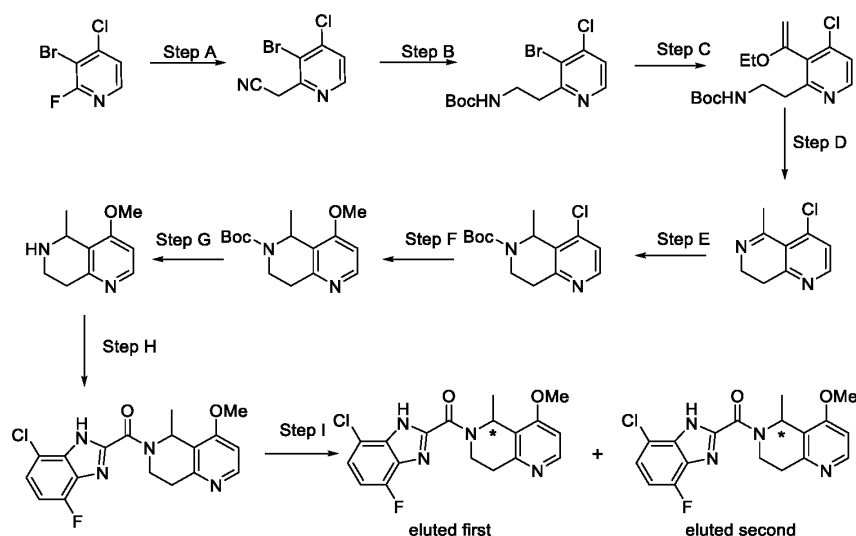
[00759] Step G: The product was dissolved in MeOH (2.00 mL), and the resulting solution was purified by chiral SFC (column: DAICEL CHIRALCEL OJ (250mm x 30mm, 10μm); mobile phase: [CO₂-MeOH]; B%:20%, isocratic elution mode). First eluted compound: LC-MS: 417.0 [M+H]⁺. ¹H NMR (400 MHz, CDCl₃) δ 10.32 (br s, 1H), 8.85 (d, J = 2.6 Hz, 1H), 7.61 - 7.28 (m, 1H), 7.06 - 5.05 (m, 3H), 4.09 - 3.90 (m, 3H), 3.85 - 3.34 (m, 1H), 3.28 - 3.02 (m, 2H). Second eluted compound: LC-MS: 417.0 [M+H]⁺. ¹H NMR (400 MHz, CDCl₃) δ 10.37 (br d, J = 2.5 Hz, 1H), 8.85 (d, J = 2.9 Hz, 1H), 7.46 - 7.27 (m, 1H), 7.06 - 5.04 (m, 3H), 4.08 - 3.90 (m, 3H), 3.85 - 3.36 (m, 1H), 3.30 - 3.00 (m, 2H). The absolute stereochemistry for the first and second eluted compounds was not determined.

Example 204: (R)-(7-Chloro-4-fluoro-6-methoxy-1H-benzo[d]imidazol-2-yl)(5-methyl-7,8-dihydro-1,6-naphthyridin-6(5H)-yl)methanone



[00760] Step A: To a solution of 7-chloro-4-fluoro-6-methoxy-1H-benzimidazole-2-carboxylic acid (100 mg, 0.409 mmol) and (5R)-5-methyl-5,6,7,8-tetrahydro-1,6-naphthyridine (75.5 mg, 0.409 mmol, HCl salt) in DCM (2.00 mL) was added TEA (248 mg, 2.45 mmol) and BOP-Cl (156 mg, 0.613 mmol). The mixture was stirred at 20 °C for 1 h. The reaction mixture was poured into H₂O (5.00 mL) and extracted with DCM (5.00 mL x 3). The combined organic layers were dried over Na₂SO₄, filtered, and concentrated under vacuum to give a residue which was purified by preparative HPLC (Waters Xbridge Prep OBD C18 column 150 × 40mm × 10μm); flow rate: 25 mL/min; gradient: 25% – 65% B over 8 min; mobile phase A: 10 mM aqueous NH₄HCO₃, mobile phase B: acetonitrile) to give (R)-(7-chloro-4-fluoro-6-methoxy-1H-benzo[d]imidazol-2-yl)(5-methyl-7,8-dihydro-1,6-naphthyridin-6(5H)-yl)methanone. LC-MS: 375.1 [M+H]⁺. ¹H NMR (400 MHz, DMSO-d₆) δ 13.99 – 13.47 (m, 1H), 8.59 – 8.25 (m, 1H), 7.89 – 7.56 (m, 1H), 7.39 – 7.09 (m, 2H), 5.71 (q, J = 6.9 Hz, 1H), 5.35 – 4.51 (m, 1H), 3.93 – 3.83 (m, 3H), 3.74 – 3.36 (m, 1H), 3.22 – 2.92 (m, 2H), 1.73 – 1.44 (m, 3H).

Examples 205A and 205B: (R) or (S)-(7-Chloro-4-fluoro-1H-benzo[d]imidazol-2-yl)(4-methoxy-5-methyl-7,8-dihydro-1,6-naphthyridin-6(5H)-yl)methanone and (R) or (S)-(7-Chloro-4-fluoro-1H-benzo[d]imidazol-2-yl)(4-methoxy-5-methyl-7,8-dihydro-1,6-naphthyridin-6(5H)-yl)methanone



[00761] Step A: To a solution of LiHMDS (1 M, 19.0 mL) in THF (40.0 mL) was added dropwise acetonitrile (780 mg, 19.0 mmol,) at -78°C under N_2 . After addition, the mixture was stirred at this temperature for 1 h, and then 3-bromo-4-chloro-2-fluoropyridine (2.00 g, 9.50 mmol) in THF (4.00 mL) was added dropwise at -78°C , and the mixture was stirred at this temperature for 1 h then was stirred at 20°C for 1 h under N_2 . The reaction mixture was added to saturated aqueous NH_4Cl (50.0 mL) and extracted with EtOAc (50.0 mL x 3). The combined organic layers were dried over Na_2SO_4 , and concentrated under reduced pressure to give a residue which was purified by flash silica gel chromatography using a gradient of EtOAc/petroleum ether from 0/1 to 1/10 to give 2-(3-bromo-4-chloropyridin-2-yl)acetonitrile. LC-MS: 231.0 $[\text{M}+\text{H}]^+$. ^1H NMR (400 MHz, CDCl_3) δ 8.45 (d, $J = 5.3$ Hz, 1H), 7.42 (d, $J = 5.3$ Hz, 1H), 4.16 (s, 2H).

[00762] Step B: To a solution of Raney-Ni (0.426 mg) in MeOH (20.0 mL) was added 2-(3-bromo-4-chloropyridin-2-yl)acetonitrile (0.500 g, 2.16 mmol) and Boc_2O (0.519 mg, 2.38 mmol) at 20°C . Then the reaction mixture was stirred at 20°C for 1 h under H_2 (15 Psi). The reaction mixture was filtered, and the filtrate was concentrated under vacuum. The residue was purified by flash silica gel chromatography using a gradient of EtOAc/petroleum ether from 0/1 to 1/3 to give tert-butyl (2-(3-bromo-4-chloropyridin-2-yl)ethyl)carbamate. LC-MS: 335.0 $[\text{M}+\text{H}]^+$. ^1H NMR (400 MHz, CDCl_3) δ 8.35 (d, $J = 5.1$ Hz, 1H), 7.29 (d, $J = 5.3$ Hz, 1H), 5.25 – 5.09 (m, 1H), 3.63 (br d, $J = 5.4$ Hz, 2H), 3.19 (t, $J = 6.1$ Hz, 2H), 1.44 (s, 8H).

[00763] Step C: To a mixture of tert-butyl (2-(3-bromo-4-chloropyridin-2-yl)ethyl)carbamate (150 mg, 0.447 mmol) and tributyl(1-ethoxyvinyl)stannane (323 mg, 0.894 mmol) in dioxane (8.00 mL) was added $\text{Pd}(\text{PPh}_3)_2\text{Cl}_2$ (31.4 mg, 0.045 mmol). The mixture was stirred at 90°C for

2 h under a N₂ atmosphere. The mixture was filtered, and the filtrate was concentrated under vacuum to give a residue which was purified by preparative TLC (petroleum ether: EtOAc=2:1, R_f= 0.35) to give tert-butyl (2-(4-chloro-3-(1-ethoxyvinyl)pyridin-2-yl)ethyl)carbamate. LC-MS: 327.2 [M+H]⁺.

[00764] Step D: To a mixture of tert-butyl (2-(4-chloro-3-(1-ethoxyvinyl)pyridin-2-yl)ethyl)carbamate (120 mg, 0.367 mmol) in EtOAc (2.00 mL) was added HCl/EtOAc (4 M, 5.00 mL). The mixture was stirred at 20 °C for 1 h under a N₂ atmosphere. The mixture was concentrated under vacuum at 30 °C to give 4-chloro-5-methyl-7,8-dihydro-1,6-naphthyridine. LC-MS: 181.1 [M+H]⁺.

[00765] Step E: To a solution of 4-chloro-5-methyl-7,8-dihydro-1,6-naphthyridine (120 mg, 0.553 mmol) in MeOH (5.00 mL) was added Boc₂O (181 mg, 0.829 mmol) and NaBH₄ (46.0 mg, 1.22 mmol) at 0 °C. The mixture was stirred at 20 °C for 2 h under a N₂ atmosphere. The reaction mixture was quenched by saturated NH₄Cl solution (5.00 mL) and extracted with EtOAc (5.00 mL × 3). The combined organic phases were washed with brine (5.00 mL × 1), dried over anhydrous Na₂SO₄, filtered and concentrated give a residue which was purified by preparative TLC (pure EtOAc, R_f= 0.53) to give tert-butyl 4-chloro-5-methyl-7,8-dihydro-1,6-naphthyridine-6(5H)-carboxylate. LC-MS: 283.2 [M+H]⁺. ¹H NMR (400 MHz, CDCl₃) δ 8.32 (br s, 1H), 7.21 (d, J= 5.3 Hz, 1H), 5.76 - 5.30 (m, 1H), 4.46 - 4.02 (m, 1H), 3.51 - 3.30 (m, 1H), 3.17 - 2.90 (m, 2H), 1.53 - 1.48 (m, 12H).

[00766] Step F: To a solution of tert-butyl 4-chloro-5-methyl-7,8-dihydro-1,6-naphthyridine-6(5H)-carboxylate (168 mg, 0.594 mmol) in DMSO (4.00 mL) was added NaOMe (320 mg, 5.94 mmol) at 20 °C. The reaction mixture was stirred at 100 °C for 2 h. The reaction mixture was concentrated. The residue was diluted with H₂O (20.0 mL) and extracted with EtOAc (20.0 mL × 3). The combined organic layers were dried over Na₂SO₄, filtered and the filtrate was concentrated to give a residue. The residue was purified by preparative TLC (SiO₂, Petroleum ether/Ethyl acetate=1/1) to give tert-butyl 4-methoxy-5-methyl-7,8-dihydro-1,6-naphthyridine-6(5H)-carboxylate. LC-MS: 279.2 [M+H]⁺.

[00767] Step G: A solution of tert-butyl 4-methoxy-5-methyl-7,8-dihydro-1,6-naphthyridine-6(5H)-carboxylate (70.0 mg, 0.251 mmol) in HCl/EtOAc (4 M, 2.00 mL) was stirred at 20 °C for 1 h. The reaction mixture was concentrated to give 4-methoxy-5-methyl-5,6,7,8-tetrahydro-1,6-naphthyridine, which was used in next step directly. LC-MS: 179.1 [M+H]⁺.

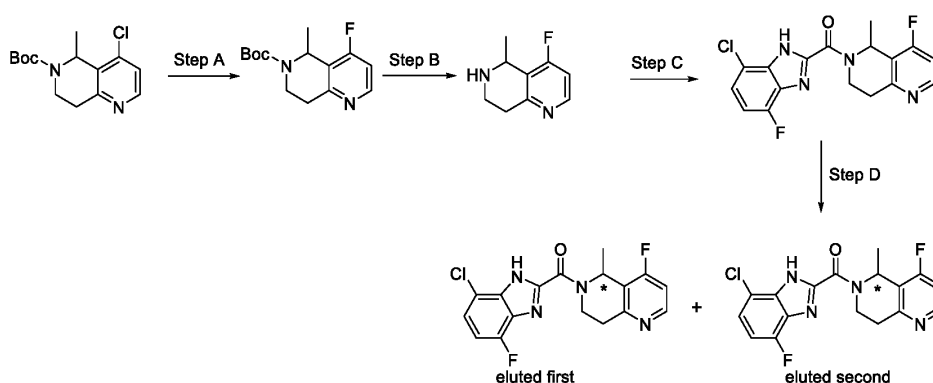
[00768] Step H: To a solution of 4-methoxy-5-methyl-5,6,7,8-tetrahydro-1,6-naphthyridine (70.0 mg, 0.392 mmol) in DCM (7.00 mL) was added BOP-Cl (199 mg, 0.785 mmol), TEA (119 mg, 1.18 mmol) and 7-chloro-4-fluoro-1H-benzimidazole-2-carboxylic acid (84.2 mg, 0.392

mmol). The reaction mixture was stirred at 20 °C for 1 h. The reaction mixture was concentrated. The residue was diluted with H₂O (15.0 mL) and extracted with EtOAc (15.0 mL × 3). The combined organic layers were dried over Na₂SO₄, filtered and the filtrate was concentrated. The residue was purified by preparative TLC (SiO₂, dichloromethane: methanol=10/1) to give (7-chloro-4-fluoro-1H-benzo[d]imidazol-2-yl)(4-methoxy-5-methyl-7,8-dihydro-1,6-naphthyridin-6(5H)-yl)methanone.

LC-MS: 375.1 [M+H]⁺.

[00769] Step I: (7-Chloro-4-fluoro-1H-benzo[d]imidazol-2-yl)(4-methoxy-5-methyl-7,8-dihydro-1,6-naphthyridin-6(5H)-yl)methanone (20.0 mg, 0.053 mmol) was further separated by SFC separation DAICEL CHIRALPAK IG (250mm x 30mm,10um); flow rate: 70 mL/min; gradient: 50% B over 13 min; mobile phase A: CO₂, mobile phase B: EtOH (0.2% CO₂(7M in MeOH)). First eluted compound: LC-MS: 375.1 [M+H]⁺. ¹H NMR (400 MHz, DMSO-d₆) δ 14.37 – 13.72 (m, 1H), 8.27 (dd, *J* = 4.9, 6.9 Hz, 1H), 7.45 – 7.27 (m, 1H), 7.23 – 6.99 (m, 2H), 5.98 – 4.70 (m, 1H), 4.67 – 3.87 (m, 1H), 3.57 (br d, *J* = 10.0 Hz, 1H), 3.17 – 2.93 (m, 2H), 2.39 – 2.27 (m, 3H), 1.52 (dd, *J* = 6.7, 14.7 Hz, 3H). Second eluted compound: LC-MS: 375.1 [M+H]⁺. ¹H NMR (400 MHz, DMSO-d₆) δ 13.82 – 13.52 (m, 1H), 8.40 – 8.26 (m, 1H), 7.32 (dd, *J* = 4.0, 8.5 Hz, 1H), 7.18 – 7.05 (m, 1H), 6.99 – 6.88 (m, 1H), 6.24 – 5.76 (m, 1H), 4.97 – 4.62 (m, 1H), 3.97 – 3.83 (m, 3H), 3.80 – 3.43 (m, 1H), 3.02 – 2.86 (m, 2H), 1.60 – 1.50 (m, 3H). The absolute stereochemistry for the first and second eluted compounds was not determined.

Examples 206A and 206B: (R) or (S)-(7-Chloro-4-fluoro-1H-benzo[d]imidazol-2-yl)(4-fluoro-5-methyl-7,8-dihydro-1,6-naphthyridin-6(5H)-yl)methanone and (R) or (S)-(7-Chloro-4-fluoro-1H-benzo[d]imidazol-2-yl)(4,5-dimethyl-7,8-dihydro-1,6-naphthyridin-6(5H)-yl)methanone



[00770] Step A: To a solution of tert-butyl 4-chloro-5-methyl-7,8-dihydro-1,6-naphthyridine-6(5H)-carboxylate (200 mg, 0.707 mmol) in DMSO (16.0 mL) was added 18-crown-6 (37.4 mg, 0.141 mmol), TBAC (39.3 mg, 0.141 mmol) and CsF (1.07 g, 7.07 mmol) at 20 °C under

nitrogen. The mixture was stirred at 140 °C for 12 h. The combined mixture was poured into H₂O (30.0 mL) and extracted with EtOAc (15.0 mL x 3). The combined organic layers were dried over Na₂SO₄, filtered and concentrated under vacuum to give a residue which was purified by preparative TLC (petroleum ether: EtOAc=1:1, R_f= 0.43) to give tert-butyl 4-fluoro-5-methyl-7,8-dihydro-1,6-naphthyridine-6(5H)-carboxylate. LC-MS: 267.2 [M+H]⁺. ¹H NMR (400 MHz, CDCl₃) δ 8.41 (br s, 1H), 6.89 (dd, J=5.5, 9.4 Hz, 1H), 5.66 – 5.25 (m, 1H), 4.45 – 4.17 (m, 1H), 3.41 – 3.16 (m, 1H), 3.12 – 2.89 (m, 2H), 1.51 (s, 9H), 1.46 (d, J=6.6 Hz, 3H).

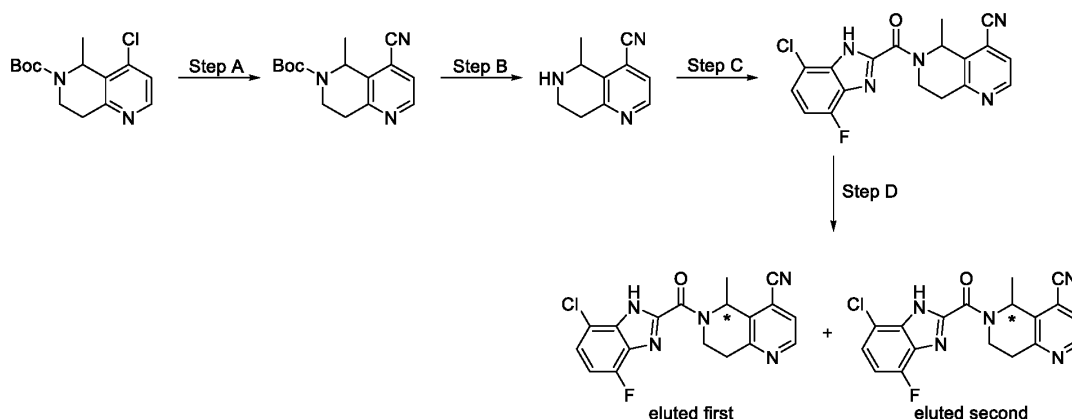
[00771] Step B: To a solution of tert-butyl 4-fluoro-5-methyl-7,8-dihydro-1,6-naphthyridine-6(5H)-carboxylate (25.0 mg, 0.094 mmol) in EtOAc (0.100 mL) was added HCl/EtOAc (4 M, 4.00 mL) at 20 °C under nitrogen. The mixture was stirred at 20 °C for 4 h. The mixture was concentrated under vacuum at 20 °C to give 4-fluoro-5-methyl-5,6,7,8-tetrahydro-1,6-naphthyridine (HCl salt). LC-MS: 167.2 [M+H]⁺.

[00772] Step C: A mixture of 4-fluoro-5-methyl-5,6,7,8-tetrahydro-1,6-naphthyridine (20.0 mg, 0.099 mmol, HCl), 7-chloro-4-fluoro-1H-benzo[d]imidazole-2-carboxylic acid (21.2 mg, 0.099 mmol), DIEA (31.9 mg, 0.246 mmol) and HATU (41.3 mg, 0.108 mmol) in DMF (2.00 mL) was stirred at 20 °C for 2 h. The reaction mixture was poured into H₂O (6.00 mL) and extracted with EtOAc (3.00 mL x 3). The combined organic layers were dried over Na₂SO₄, filtered and concentrated under reduced pressure. The residue was purified by preparative TLC (petroleum ether: EtOAc=0:1, R_f= 0.36) to give (7-chloro-4-fluoro-1H-benzo[d]imidazol-2-yl)(4-fluoro-5-methyl-7,8-dihydro-1,6-naphthyridin-6(5H)-yl)methanone. LC-MS: 363.1 [M+H]⁺.

[00773] Step D: (7-Chloro-4-fluoro-1H-benzo[d]imidazol-2-yl)(4-fluoro-5-methyl-7,8-dihydro-1,6-naphthyridin-6(5H)-yl)methanone (30.0 mg) was further separated by SFC separation column: DAICEL CHIRALPAK IG (250mm*30mm,10um);mobile phase: [CO₂-MeOH (0.1%NH₃H₂O)]; B%:50%, isocratic elution mode. First eluted compound: LC-MS: 363.1 [M+H]⁺. ¹H NMR (400 MHz, DMSO-*d*₆) δ 14.13 (br s, 1H), 8.47 (ddd, J=5.6, 8.4, 13.6 Hz, 1H), 7.43 – 7.03 (m, 3H), 5.91 – 4.69 (m, 1H), 3.85 – 3.43 (m, 1H), 3.41 – 3.33 (m, 1H), 3.29 – 3.06 (m, 1H), 3.05 – 2.95 (m, 1H), 1.70 – 1.54 (m, 3H). Second eluted compound: LC-MS: 363.1 [M+H]⁺. ¹H NMR (400 MHz, DMSO-*d*₆) δ 14.12 (br s, 1H), 8.48 (ddd, J=5.5, 8.3, 13.6 Hz, 1H), 7.48 – 7.02 (m, 3H), 5.94 – 4.70 (m, 1H), 3.86 – 3.43 (m, 1H), 3.35 (br s, 1H), 3.30 – 3.08 (m, 1H), 3.07 – 2.97 (m, 1H), 1.72 – 1.54 (m, 3H). The absolute stereochemistry for the first and second eluted compounds was not determined.

Examples 207A and 207B: (R) or (S)-6-(7-Chloro-4-fluoro-1H-benzo[d]imidazole-2-carbonyl)-5-methyl-5,6,7,8-tetrahydro-1,6-naphthyridine-4-carbonitrile and (R) or (S)-6-(7-

Chloro-4-fluoro-1H-benzo[d]imidazole-2-carbonyl)-5-methyl-5,6,7,8-tetrahydro-1,6-naphthyridine-4-carbonitrile



[00774] Step A: To a solution of tert-butyl 4-chloro-5-methyl-7,8-dihydro-5H-1,6-naphthyridine-6-carboxylate (50.0 mg, 0.176 mmol) and $\text{Zn}(\text{CN})_2$ (41.5 mg, .353 mmol) in DMA (2.00 mL) was added BrettPhos Pd G₃ (32.0 mg, 0.353 mmol) under a nitrogen atmosphere. The mixture was stirred at 120 °C for 8 h. The reaction mixture was poured into H_2O (5.00 mL) and extracted with EtOAc (3.00 mL x 4). The combined organic layers were dried over Na_2SO_4 , filtered and concentrated under vacuum to give a residue which was purified by preparative TLC (petroleum ether: EtOAc = 1:1) to give tert-butyl 4-cyano-5-methyl-7,8-dihydro-5H-1,6-naphthyridine-6(5H)-carboxylate. ^1H NMR (400 MHz, CDCl_3) δ 8.59 (br s, 1H), 7.39 (d, J =4.8 Hz, 1H), 5.39 – 5.77 (m, 1H), 3.28 – 4.49 (m, 2H), 2.97 – 3.18 (m, 2H), 1.59 (br d, J =6.8 Hz, 3H), 1.52 (s, 9H). LC-MS: 274.2 $[\text{M}+\text{H}]^+$.

[00775] Step B: To a solution of tert-butyl 4-cyano-5-methyl-7,8-dihydro-5H-1,6-naphthyridine-6-carboxylate (18.0 mg, 0.658 mmol) in EtOAc (1.00 mL) was added HCl/EtOAc (4 M, 1.50 mL). The mixture was stirred at 20 °C for 5 h. The reaction mixture was concentrated under reduced pressure to give 5-methyl-5,6,7,8-tetrahydro-1,6-naphthyridine-4-carbonitrile. LC-MS: 174.2 $[\text{M}+\text{H}]^+$.

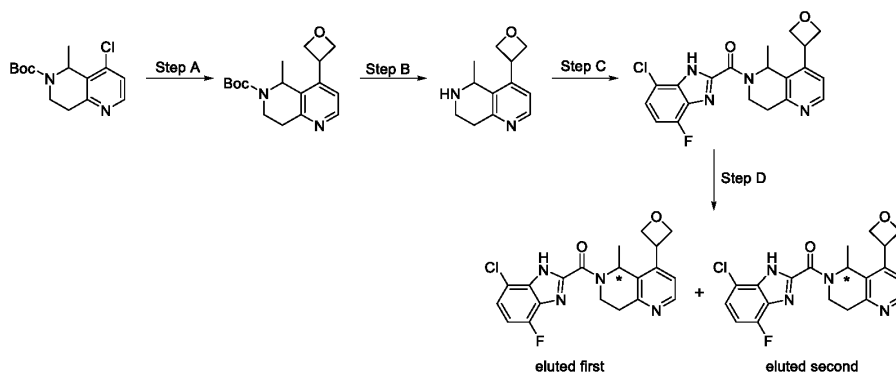
[00776] Step C: To a solution of 5-methyl-5,6,7,8-tetrahydro-1,6-naphthyridine-4-carbonitrile (18.0 mg, 0.858 mmol,) and 7-chloro-4-fluoro-1H-benzimidazole-2-carboxylic acid (18.4 mg, 0.858 mmol) in DMF (1.00 mL) was added HATU (42.3 mg, 1.11 mmol) and DIEA (33.29 mg, 0.257 mmol). The mixture was stirred at 20 °C for 2 h. The reaction mixture was poured into H_2O (5.00 mL) and extracted with EtOAc (3.00 mL x 4). The combined organic layers were dried over Na_2SO_4 , filtered, and concentrated under vacuum to give a residue which was purified by preparative TLC (petroleum ether: EtOAc = 1 : 1, R_f = 0.43) to give 6-(7-Chloro-4-fluoro-1H-

benzo[d]imidazole-2-carbonyl)-5-methyl-5,6,7,8-tetrahydro-1,6-naphthyridine-4-carbonitrile. LC-MS: 370.2 [M+H]⁺.

[00777] Step D: 6-(7-Chloro-4-fluoro-1H-benzo[d]imidazole-2-carbonyl)-5-methyl-5,6,7,8-tetrahydro-1,6-naphthyridine-4-carbonitrile (25.0 mg, crude) was further separated by SFC separation DAICEL CHIRALPAK IH (250 × 30 mm, 10 μm); flow rate: 30 mL/min; gradient: 30% B over 14 min; mobile phase A: heptane, mobile phase B: CO₂ – IPA (0.1% NH₃H₂O). First eluted compound: LC-MS: 370.1 [M+H]⁺. ¹H NMR (400 MHz, DMSO-*d*₆) δ 13.93 – 14.34 (m, 1H), 8.59 – 8.78 (m, 1H), 7.64 – 7.89 (m, 1H), 7.35 (br dd, *J* = 8.1, 3.0 Hz, 1H), 7.16 (br t, *J* = 9.3 Hz, 1H), 5.95 (q, *J* = 6.8 Hz, 1H), 4.65–5.30 (m, 1H), 3.49 – 3.98 (m, 1H), 3.05–3.27 (m, 2H), 1.60 – 1.85 (m, 3H).

Second eluted compound: LC-MS: 370.1 [M+H]⁺. ¹H NMR (400 MHz, DMSO-*d*₆) δ 13.92 – 14.31 (m, 1H), 8.50 – 8.83 (m, 1H), 7.72 – 7.94 (m, 1H), 7.25 – 7.42 (m, 1H), 7.16 (br t, *J* = 9.3 Hz, 1H), 5.95 (q, *J* = 6.8 Hz, 1H), 4.64 – 5.28 (m, 1H), 3.50 – 4.08 (m, 1H), 3.04 – 3.27 (m, 2H), 1.67 (d, *J* = 6.8 Hz, 2H), 1.77 (d, *J* = 6.8 Hz, 1H). The absolute stereochemistry for the first and second eluted compounds was not determined.

Examples 208A and 208B: (R) or (S)-(7-Chloro-4-fluoro-1H-benzo[d]imidazol-2-yl)(5-methyl-4-(oxetan-3-yl)-7,8-dihydro-1,6-naphthyridin-6(5H)-yl)methanone and (R) or (S)-(7-Chloro-4-fluoro-1H-benzo[d]imidazol-2-yl)(5-methyl-4-(oxetan-3-yl)-7,8-dihydro-1,6-naphthyridin-6(5H)-yl)methanone



[00778] Step A: A mixture of tert-butyl 4-chloro-5-methyl-7,8-dihydro-1,6-naphthyridine-6(5H)-carboxylate (300 mg, 1.1 mmol), oxetan-3-ol (290 mg, 2.1 mmol), bis[3,5-difluoro-2-[5-(trifluoromethyl)-2-pyridyl]phenyl] iridium(1+); 4-tert-butyl-2-(4-tert-butyl-2-pyridyl)pyridine; hexafluorophosphate (12.0 mg, 0.01 mmol), NiCl₂ glyme (12.0 mg, 0.05 mmol) and 4-tert-butyl-2-(4-tert-butyl-2-pyridyl) pyridine (14.0 mg, 0.05 mmol), TTMS (264 mg, 1.1 mmol), Na₂CO₃ (225 mg, 2.10 mmol) in DME (10.00 mL) was stirred at 20 °C for 12 h under argon atmosphere with 34 W blue LED. The mixture was filtered, and concentrated under

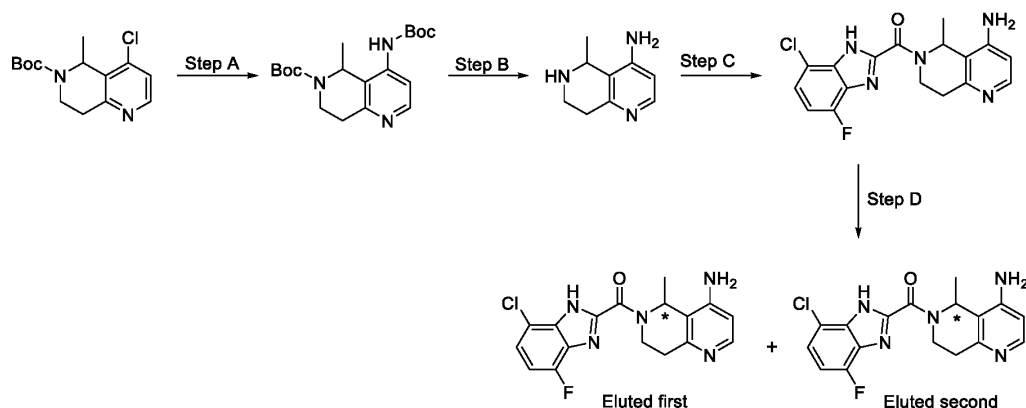
vacuum to give a residue which was purified by preparative TLC (petroleum ether: EtOAc = 0:1, R_f = 0.38) to give tert-butyl 5-methyl-4-(oxetan-3-yl)-7,8-dihydro-1,6-naphthyridine-6(5H)-carboxylate. LC-MS: 305.2 $[M+H]^+$.

[00779] Step B: To a mixture of tert-butyl 5-methyl-4-(oxetan-3-yl)-7,8-dihydro-1,6-naphthyridine-6(5H)-carboxylate (45.0 mg, 0.14 mmol) in DCM (2.00 mL) was added TFA (150 mg, 1.30 mmol). The mixture was stirred at 20 °C for 2 h. The mixture was concentrated under vacuum at 30 °C to give 5-methyl-4-(oxetan-3-yl)-5,6,7,8-tetrahydro-1,6-naphthyridine (29 mg, crude). LC-MS: 205.1 $[M+H]^+$.

[00780] Step C: A mixture of 7-chloro-4-fluoro-1H-benzo[d]imidazole-2-carboxylic acid (27.3 mg, 0.127 mmol), HATU (48.4 mg, 0.127 mmol), DIEA (50.0 mg, 0.382 mmol) and 5-methyl-4-(oxetan-3-yl)-5,6,7,8-tetrahydro-1,6-naphthyridine (26.0 mg, 0.127 mmol) in DMF (2.00 mL) was stirred at 20 °C for 12 h. The mixture was concentrated under vacuum at 30 °C to give a residue which was purified by preparative HPLC (Waters Xbridge Prep OBD C18 column (150 × 40 mm, 10 μ m); flow rate: 25 mL/min; gradient: 20% – 50% B over 8 min; mobile phase A: water (10 mM NH_4HCO_3), mobile phase B: acetonitrile) to give (7-chloro-4-fluoro-1H-benzo[d]imidazol-2-yl)(5-methyl-4-(oxetan-3-yl)-7,8-dihydro-1,6-naphthyridin-6(5H)-yl)methanone. LC-MS: 401.1 $[M+H]^+$.

[00781] Step D: (7-Chloro-4-fluoro-1H-benzo[d]imidazol-2-yl)(5-methyl-4-(oxetan-3-yl)-7,8-dihydro-1,6-naphthyridin-6(5H)-yl)methanone (20.0 mg) was further separated by SFC separation ChiralPak IH (250 × 30 mm, 10 μ m); flow rate: 3.4 mL/min; gradient: 50% B over 14 min; mobile phase A: heptane, mobile phase B: CO_2 – MeOH (0.1% NH_3H_2O). First eluted compound: LC-MS: 401.1 $[M+H]^+$. 1H NMR (400 MHz, $DMSO-d_6$) δ 14.12 – 12.91 (m, 1H), 8.55 – 8.41 (m, 1H), 7.65 – 7.36 (m, 1H), 7.33 – 7.06 (m, 2H), 6.68 – 5.59 (m, 1H), 5.12 (s, 1H), 4.97 – 4.80 (m, 1H), 4.79 – 4.63 (m, 2H), 4.62 – 4.48 (m, 2H), 4.02 – 3.59 (m, 1H), 3.23 – 3.10 (m, 2H), 1.46 (br dd, J = 6.3, 15.3 Hz, 3H). Second eluted compound: LC-MS: 401.1 $[M+H]^+$. 1H NMR (400 MHz, $DMSO-d_6$) δ 13.95 – 13.53 (m, 1H), 8.48 (br dd, J = 4.5, 12.9 Hz, 1H), 7.66 – 7.06 (m, 3H), 6.65 – 5.67 (m, 1H), 5.16 – 5.00 (m, 1H), 4.98 – 4.81 (m, 1H), 4.78 – 4.63 (m, 2H), 4.61 – 4.49 (m, 2H), 4.02 – 3.61 (m, 1H), 3.19 – 3.07 (m, 2H), 1.47 (br dd, J = 6.2, 16.8 Hz, 3H). The absolute stereochemistry for the first and second eluted compounds was not determined.

Examples 209A and 209B: (R) or (S)-(4-Amino-5-methyl-7,8-dihydro-1,6-naphthyridin-6(5H)-yl)(7-chloro-4-fluoro-1H-benzo[d]imidazol-2-yl)methanone and (R) or (S)-(4-Amino-5-methyl-7,8-dihydro-1,6-naphthyridin-6(5H)-yl)(7-chloro-4-fluoro-1H-benzo[d]imidazol-2-yl)methanone



[00782] Step A: To a mixture of tert-butyl 4-chloro-5-methyl-7,8-dihydro-1,6-naphthyridine-6(5H)-carboxylate (150 mg, 0.531 mmol) and NH_2Boc (93.2 mg, 0.796 mmol) in dioxane (6.00 mL) was added Brettphos (57.0 mg, 0.106 mmol), BrettPhos Pd G3 (96.2 mg, 0.106 mmol) and Cs_2CO_3 (346 mg, 1.06 mmol). The mixture was degassed and purged with nitrogen three times and stirred at 100 °C for 12 h under nitrogen atmosphere. The reaction mixture was concentrated under vacuum to give a residue which was purified by flash silica gel chromatography using a gradient of EtOAc/petroleum ether from 0/1 to 1/1 to give tert-butyl 4-((tert-butoxycarbonyl)amino)-5-methyl-7,8-dihydro-1,6-naphthyridine-6(5H)-carboxylate. LC-MS: 364.2 $[\text{M}+\text{H}]^+$. ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ 9.14 – 8.94 (m, 1H), 8.24 (br d, $J = 3.3$ Hz, 1H), 7.48 – 7.14 (m, 1H), 5.64 – 5.36 (m, 1H), 4.00 – 3.82 (m, 1H), 3.50 – 3.35 (m, 1H), 2.85 (br t, $J = 5.9$ Hz, 2H), 1.46 (d, $J = 15.8$ Hz, 18H), 1.25 (br s, 3H).

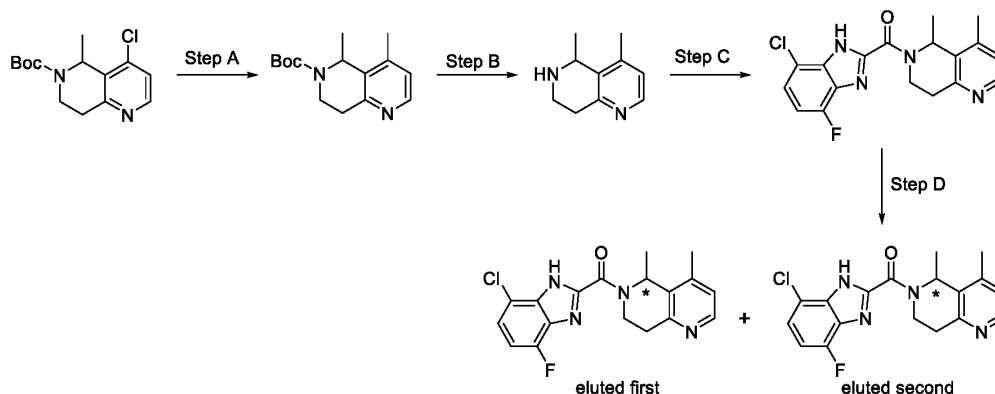
[00783] Step B: To a solution of tert-butyl 4-((tert-butoxycarbonyl)amino)-5-methyl-7,8-dihydro-1,6-naphthyridine-6(5H)-carboxylate (50.0 mg, 0.138 mmol) in EtOAc (2.00 mL) was added HCl/EtOAc (4 M, 2.50 mL), then the mixture was stirred at 20 °C for 2 h. The reaction mixture was concentrated under vacuum to give 5-methyl-5,6,7,8-tetrahydro-1,6-naphthyridin-4-amine (25.0 mg, 91%, HCl). LC-MS: 164.3 $[\text{M}+\text{H}]^+$.

[00784] Step C: To a solution of 5-methyl-5,6,7,8-tetrahydro-1,6-naphthyridin-4-amine (25.0 mg, 0.125 mmol, HCl) and 7-chloro-4-fluoro-1H-benzo[d]imidazole-2-carboxylic acid (26.9 mg, 0.125 mmol) in DMF (3.00 mL) was added HATU (47.6 mg, 0.125 mmol) and DIEA (48.5 mg, 0.376 mmol), then the mixture was stirred at 20 °C for 12 h. The mixture was treated with 2M NaOH (0.2 mL), after 0.5 h, the reaction mixture was poured into H_2O (2.00 mL) and extracted with DCM (1.00 mL x 3). The combined organic layers were dried over Na_2SO_4 , filtered, and concentrated under vacuum to give a residue which was purified by flash silica gel chromatography using a gradient of EtOAc/petroleum ether from 0/1 to 1/3 to give (4-amino-5-

methyl-7,8-dihydro-1,6-naphthyridin-6(5H)-yl)(7-chloro-4-fluoro-1H-benzo[d]imidazol-2-yl)methanone. LC-MS: 360.2 [M+H]⁺.

[00785] Step D: (4-Amino-5-methyl-7,8-dihydro-1,6-naphthyridin-6(5H)-yl)(7-chloro-4-fluoro-1H-benzo[d]imidazol-2-yl)methanone (30.0 mg, 0.060 mmol) was further separated by SFC separation ChiralPak IH (250 × 30 mm, 10 μm); flow rate: 70 mL/min; gradient: 50% B over 11 min; mobile phase A: heptane, mobile phase B: CO₂ – MeOH (0.1% NH₃H₂O). First eluted compound: LC-MS: 360.1 [M+H]⁺. ¹H NMR (400 MHz, DMSO-d₆) δ 7.85 (d, *J* = 5.4 Hz, 1H), 7.29 (br d, *J* = 2.3 Hz, 1H), 7.09 (br t, *J* = 9.1 Hz, 1H), 6.49 – 6.36 (m, 1H), 6.17 – 5.76 (m, 2H), 5.74 – 5.28 (m, 1H), 4.82 – 4.51 (m, 1H), 3.78 – 3.40 (m, 1H), 3.15 – 2.62 (m, 2H), 1.43 (d, *J* = 6.5 Hz, 3H). Second eluted compound: LC-MS: 360.1 [M+H]⁺. ¹H NMR (400 MHz, DMSO-d₆) δ 7.85 (d, *J* = 5.6 Hz, 1H), 7.34 – 7.16 (m, 1H), 7.15 – 6.97 (m, 1H), 6.51 – 6.30 (m, 1H), 6.20 – 5.98 (m, 1H), 5.80 – 5.32 (m, 1H), 4.79 – 4.52 (m, 1H), 3.80 – 3.59 (m, 1H), 3.05 – 2.68 (m, 2H), 1.43 (d, *J* = 6.5 Hz, 3H). The absolute stereochemistry for the first and second eluted compounds was not determined.

Examples 210A and 210B: (R) or (S)-(7-Chloro-4-fluoro-1H-benzo[d]imidazol-2-yl)(4,5-dimethyl-7,8-dihydro-1,6-naphthyridin-6(5H)-yl)methanone and (R) or (S)-(7-Chloro-4-fluoro-1H-benzo[d]imidazol-2-yl)(4,5-dimethyl-7,8-dihydro-1,6-naphthyridin-6(5H)-yl)methanone



[00786] Step A: To a solution of tert-butyl 4-chloro-5-methyl-7,8-dihydro-1,6-naphthyridine-6(5H)-carboxylate (100 mg, 0.354 mmol) in 2-methylbutan-2-ol (2.00 mL) was added 2,4,6-trimethyl-1,3,5,2,4,6-trioxatriborinane (107 mg, 0.424 mmol) and P(Cy₃)Pd G3 (26.0 mg, 0.035 mmol). The mixture was degassed and purged with N₂ for three times, then Cs₂CO₃ (230 mg, 0.707 mmol) in H₂O (0.5 mL) was added into the mixture and stirred at 80 °C for 12 h under N₂ atmosphere. The reaction mixture was poured into H₂O (5.00 mL) and extracted with DCM (5.00 mL × 4). The combined organic layers were dried over Na₂SO₄, filtered, and concentrated under

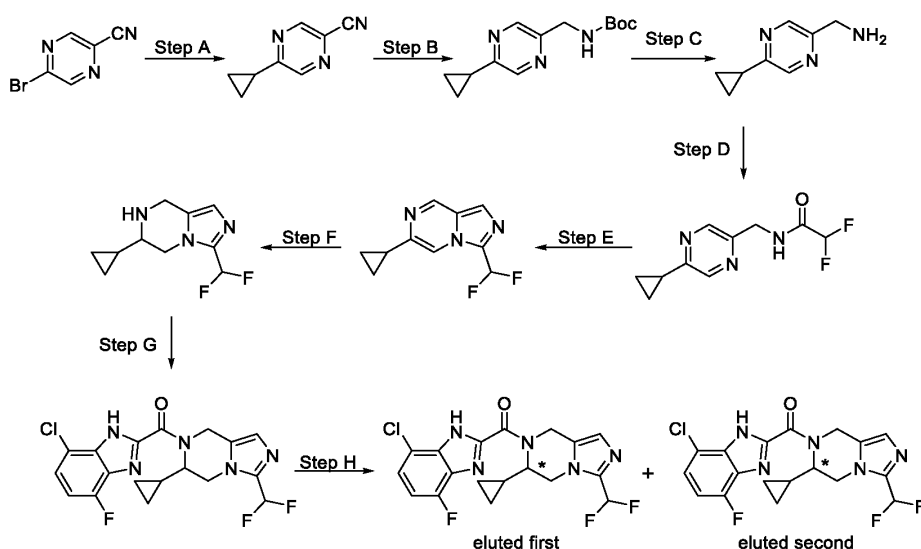
vacuum to give a residue which was purified by flash silica gel chromatography using a gradient of EtOAc/petroleum ether from 0/1 to 1/3 to give tert-butyl 4,5-dimethyl-7,8-dihydro-1,6-naphthyridine-6(5H)-carboxylate. LC-MS: 263.2 [M+H]⁺. ¹H NMR (400 MHz, CDCl₃) δ 8.28 (br d, *J* = 5.0 Hz, 1H), 7.00 – 6.85 (m, 1H), 5.57 – 5.18 (m, 1H), 4.21 – 3.99 (m, 1H), 3.60 – 3.33 (m, 1H), 3.10 – 2.94 (m, 2H), 2.36 – 2.29 (m, 3H), 1.50 (br s, 9H), 1.42 – 1.38 (m, 3H).

[00787] Step B: To a mixture of tert-butyl 4,5-dimethyl-7,8-dihydro-1,6-naphthyridine-6(5H)-carboxylate (90 mg, 0.343 mmol) in EtOAc (2.00 mL) was added HCl/EtOAc (4M, 5.00 mL). The mixture was stirred at 20 °C for 1 h. The mixture was concentrated under vacuum at 30 °C to give 4,5-dimethyl-5,6,7,8-tetrahydro-1,6-naphthyridine. LC-MS: 163.3 [M+H]⁺.

[00788] Step C: To a solution of 4,5-dimethyl-5,6,7,8-tetrahydro-1,6-naphthyridine (80 mg, 0.403 mmol) in DMF (1.00 mL) was added 7-chloro-4-fluoro-1H-benzimidazole-2-carboxylic acid (86.4 mg, 0.403 mmol), DIEA (104 mg, 0.805 mmol) and HATU (76.6 mg, 0.201 mmol). The mixture was stirred at 20 °C for 1 h. The reaction mixture was poured into H₂O (5.00 mL) and extracted with EtOAc (10.0 mL x 3). The combined organic layers were dried over Na₂SO₄, filtered and concentrated under reduced pressure to give a residue which was purified by flash silica gel chromatography using a gradient of EtOAc/petroleum ether from 1/100 to 1/3 to give (7-chloro-4-fluoro-1H-benzo[d]imidazol-2-yl)(4,5-dimethyl-7,8-dihydro-1,6-naphthyridin-6(5H)-yl)methanone. LC-MS: 359.1 [M+H]⁺.

[00789] Step D: (7-Chloro-4-fluoro-1H-benzo[d]imidazol-2-yl)(4,5-dimethyl-7,8-dihydro-1,6-naphthyridin-6(5H)-yl)methanone (50.0 mg, 0.139 mmol) was further separated by SFC separation ChiralPak IH (250 × 30 mm, 10 μm); flow rate: 30 mL/min; gradient: 45% B over 14 min; mobile phase A: heptane, mobile phase B: CO₂ – MeOH (0.1% NH₃H₂O). First eluted compound: LC-MS: 359.1 [M+H]⁺. ¹H NMR (400 MHz, DMSO-*d*₆) δ 14.37 – 13.72 (m, 1H), 8.27 (dd, *J* = 4.9, 6.9 Hz, 1H), 7.45 – 7.27 (m, 1H), 7.23 – 6.99 (m, 2H), 5.98 – 4.70 (m, 1H), 4.67 – 3.87 (m, 1H), 3.57 (br d, *J* = 10.0 Hz, 1H), 3.17 – 2.93 (m, 2H), 2.39 – 2.27 (m, 3H), 1.52 (dd, *J* = 6.7, 14.7 Hz, 3H). Second eluted compound: LC-MS: 359.1 [M+H]⁺. ¹H NMR (400 MHz, DMSO-*d*₆) δ 14.33 – 13.84 (m, 1H), 8.38 – 8.23 (m, 1H), 7.38 (dt, *J* = 3.6, 9.2 Hz, 1H), 7.25 – 7.05 (m, 2H), 6.58 – 5.74 (m, 1H), 5.08 – 4.46 (m, 1H), 4.05 – 3.52 (m, 1H), 3.20 – 2.90 (m, 2H), 2.40 – 2.24 (m, 3H), 1.60 – 1.44 (m, 3H). The absolute stereochemistry for the first and second eluted compounds was not determined.

Examples 211A and 211B: (R) or (S)-(7-Chloro-4-fluoro-1H-benzo[d]imidazol-2-yl)(6-cyclopropyl-3-(difluoromethyl)-5,6-dihydroimidazo [1,5-a]pyrazin-7(8H)-yl)methanone and (R) or (S)-(7-Chloro-4-fluoro-1H-benzo[d]imidazol-2-yl)(6-cyclopropyl-3-(difluoromethyl)-5,6-dihydroimidazo[1,5-a]pyrazin-7(8H)-yl)methanone



[00790] Step A: A mixture of 5-bromopyrazine-2-carbonitrile (10.0 g, 54.4 mmol), cyclopropylboronic acid (4.67 g, 54.4 mmol), Pd(dppf)Cl₂ (3.98 g, 5.43 mmol) and Cs₂CO₃ (53.1 g, 163 mmol) in dioxane (200 mL) and H₂O (20.0 mL) was degassed and purged with nitrogen for 3 times, and then the mixture was stirred at 100 °C for 1 h under nitrogen atmosphere. The crude reaction was concentrated and then diluted with EtOAc (20.0 mL x 3) and water (10.0 mL). The organic layer was concentrated in vacuum to give a residual which was purified by flash silica gel chromatography using a gradient of EtOAc/petroleum ether from 0/1 to 1/10 to give 5-cyclopropylpyrazine-2-carbonitrile. LC-MS: 146.2 [M+H]⁺.

[00791] Step B: To a suspension of Raney-Ni (590 mg) in MeOH (10.0 mL) was added 5-cyclopropylpyrazine-2-carbonitrile (1.00 g, 6.89 mmol) and Boc₂O (1.50 g, 6.89 mmol) under nitrogen atmosphere. The suspension was degassed and purged with hydrogen for 3 times. The mixture was stirred under hydrogen (15 Psi) at 20 °C for 2 h. The mixture was filtered on celite. The filtrate was concentrated in vacuum to give a residue which was purified by flash silica gel chromatography using a gradient of EtOAc/petroleum ether from 0/1 to 1/5 to give tert-butyl ((5-cyclopropylpyrazin-2-yl)methyl)carbamate. LC-MS: 250.3 [M+H]⁺.

[00792] Step C: A mixture of tert-butyl ((5-cyclopropylpyrazin-2-yl)methyl)carbamate (1.10 g, 4.41 mmol) in 4M HCl/EtOAc (10.0 mL) was stirred at 20 °C for 0.5 h. The reaction mixture was concentrated under reduced pressure to give (5-cyclopropylpyrazin-2-yl)methanamine. LC-MS: 150.1 [M+H]⁺.

[00793] Step D: To a solution of (5-cyclopropylpyrazin-2-yl)methanamine (950 mg, 6.37 mmol) in DCM (10.0 mL) was added dropwise (2,2-difluoroacetyl) 2,2-difluoroacetate (1.33 g, 7.64 mmol) at 0 °C. After addition, the mixture was stirred at 25 °C for 1 h. The crude reaction

was concentrated and then diluted with DCM (15 mL) and water (15 mL). The organic layer was concentrated in vacuum to give a residual which was purified by flash silica gel chromatography using a gradient of EtOAc/petroleum ether from 0/1 to 1/2 to give N-((5-cyclopropylpyrazin-2-yl)methyl)-2,2-difluoroacetamide. LC-MS: 228.2 [M+H]⁺.

[00794] Step E: To a solution of N-((5-cyclopropylpyrazin-2-yl)methyl)-2,2-difluoroacetamide (750 mg, 3.30 mmol) in POCl₃ (8.00 mL) was added P₂O₅ (469 mg, 3.30 mmol, 204 µL). The mixture was stirred at 100 °C for 12 h. The crude reaction was concentrated and then diluted with EtOAc (15 mL) and water (15 mL) at 0 °C. The organic layer was concentrated in vacuum and purified by flash silica gel chromatography using a gradient of EtOAc/petroleum ether from 0/1 to 1/10 to give 6-cyclopropyl-3-(difluoromethyl)imidazo[1,5-a]pyrazine. LC-MS: 210.2 [M+H]⁺.

[00795] Step F: To a solution of PtO₂ (43.4 mg, 0.191 mmol) in AcOH (4.00 mL) was added 6-cyclopropyl-3-(difluoromethyl)imidazo[1,5-a]pyrazine (400 mg, 1.91 mmol) under nitrogen atmosphere. The suspension was degassed and purged with hydrogen for 3 times. The mixture was stirred under hydrogen (15 Psi) at 20 °C for 2 h. The reaction mixture was filtered and concentrated under reduced pressure to give 6-cyclopropyl-3-(difluoromethyl)-5,6,7,8-tetrahydroimidazo[1,5-a]pyrazine. LC-MS: 214.3 [M+H]⁺.

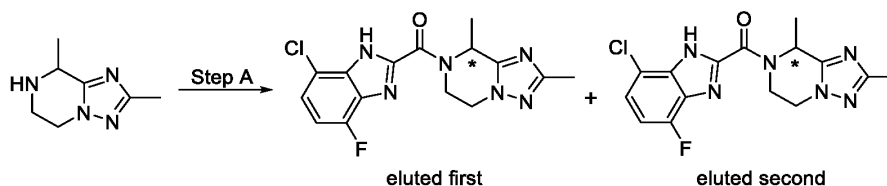
[00796] Step G: To a solution of 6-cyclopropyl-3-(difluoromethyl)-5,6,7,8-tetrahydroimidazo[1,5-a]pyrazine (340 mg, 1.59 mmol) in THF (6.00 mL) was added 7-chloro-4-fluoro-1H-benzimidazole-2-carboxylic acid (411 mg, 1.91 mmol), DIEA (515 mg, 3.99 mmol) and BOP-Cl (447 mg, 1.75 mmol). The mixture was stirred at 20 °C for 12 h. The reaction was concentrated and then diluted with EtOAc and water. The organic layer was concentrated in vacuum to give a residue which was purified by flash silica gel chromatography using a gradient of EtOAc/petroleum ether from 0/1 to 1/3 to give (7-chloro-4-fluoro-1H-benzo[d]imidazol-2-yl)(6-cyclopropyl-3-(difluoromethyl)-5,6-dihydroimidazo[1,5-a]pyrazin-7(8H)-yl)methanone. LC-MS: 410.1 [M+H]⁺.

[00797] Step H: (7-Chloro-4-fluoro-1H-benzo[d]imidazol-2-yl)(6-cyclopropyl-3-(difluoromethyl)-5,6-dihydroimidazo[1,5-a]pyrazin-7(8H)-yl)methanone (20.0 mg, 0.047 mmol) was further separated by SFC separation DAICEL CHIRALPAK IG (250 × 30 mm, 10 µm); flow rate: 70.0g/min; gradient: 38% B over 14 min; mobile phase A: CO₂, mobile phase B: EtOH (0.1% NH₃H₂O). First eluted compound: LC-MS: 410.1 [M+H]⁺. ¹H NMR (400 MHz, CDCl₃) δ 11.61 - 10.67 (m, 1H), 7.34 - 7.28 (m, 1H), 7.11 - 6.99 (m, 2H), 6.97 - 6.67 (m, 1H), 6.47 - 6.17 (m, 1H), 5.75 - 5.18 (m, 1H), 4.83 - 4.55 (m, 2H), 4.49 - 4.22 (m, 1H), 1.23 - 1.09 (m, 1H), 0.85 - 0.42 (m, 4H). Second eluted compound: LC-MS: 410.2 [M+H]⁺. ¹H NMR (400 MHz, CDCl₃) δ

11.83 - 10.67 (m, 1H), 7.34 - 7.28 (m, 1H), 7.13 - 6.99 (m, 2H), 6.99 - 6.67 (m, 1H), 6.48 - 6.15 (m, 1H), 5.78 - 5.14 (m, 1H), 4.84 - 4.57 (m, 2H), 4.49 - 4.22 (m, 1H), 1.20 - 1.08 (m, 1H), 0.77 - 0.46 (m, 4H).

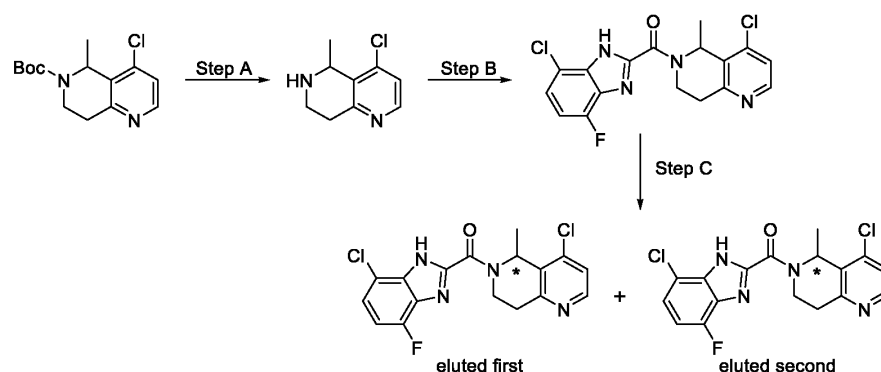
The absolute stereochemistry for the first and second eluted compounds was not determined.

Examples 212A and 212B: (R) or (S)-(7-Chloro-4-fluoro-1H-benzo[d]imidazol-2-yl)(2,8-dimethyl-5,6-dihydro-[1,2,4]triazolo[1,5-a]pyrazin-7(8H)-yl)methanone and (R) or (S)-(7-Chloro-4-fluoro-1H-benzo[d]imidazol-2-yl)(2,8-dimethyl-5,6-dihydro-[1,2,4]triazolo[1,5-a]pyrazin-7(8H)-yl)methanone



[00798] Step A: A mixture of 7-chloro-4-fluoro-1H-benzo[d]imidazole-2-carboxylic acid (84.6 mg, 0.394 mmol), 2,8-dimethyl-5,6,7,8-tetrahydro-[1,2,4]triazolo[1,5-a]pyrazine (60.0 mg, 0.394 mmol), BOP-Cl (110 mg, 0.434 mmol) and DIEA (153 mg, 1.18 mmol) in THF (2.00 mL) was stirred at 20 °C for 12 h. The mixture was concentrated under vacuum at 30 °C to give a residue which was purified by preparative HPLC (Waters Xbridge Prep OBD C18 column (150 × 40 mm, 10 μm); flow rate: 25 mL/min; gradient: 20% – 50% B over 8 min; mobile phase A: water (10 mM NH₄HCO₃), mobile phase B: acetonitrile). The lyophilized target was further purified by SFC separation DAICEL CHIRALPAK IG (250 × 30 mm, 10 μm); flow rate: 30 mL/min; gradient: 40% B over 14 min; mobile phase A: heptane, mobile phase B: CO₂ – MeOH (0.1% NH₃H₂O). First eluted compound: LC-MS: 349 [M+H]⁺. ¹H NMR (400 MHz, DMSO-*d*₆) δ 14.20 (br d, *J* = 2.5 Hz, 1H), 7.38 (br dd, *J* = 3.1, 8.1 Hz, 1H), 7.19 (br t, *J* = 9.2 Hz, 1H), 6.69 – 4.80 (m, 2H), 4.27 – 3.58 (m, 3H), 2.28 – 2.19 (m, 3H), 1.72 – 1.55 (m, 3H). Second eluted compound: LC-MS: 349 [M+H]⁺. ¹H NMR (400 MHz, DMSO-*d*₆) δ 14.20 (br s, 1H), 7.39 (dd, *J* = 3.8, 8.4 Hz, 1H), 7.19 (t, *J* = 9.3 Hz, 1H), 6.64 – 4.79 (m, 2H), 4.28 – 3.57 (m, 3H), 2.29 – 2.17 (m, 3H), 1.75 – 1.52 (m, 3H). The absolute stereochemistry for the first and second eluted compounds was not determined.

Examples 213A and 213B: (R) or (S)-(7-Chloro-4-fluoro-1H-benzo[d]imidazol-2-yl)(4-chloro-5-methyl-7,8-dihydro-1,6-naphthyridin-6(5H)-yl)methanone and (R) or (S)-(7-Chloro-4-fluoro-1H-benzo[d]imidazol-2-yl)(4-chloro-5-methyl-7,8-dihydro-1,6-naphthyridin-6(5H)-yl)methanone



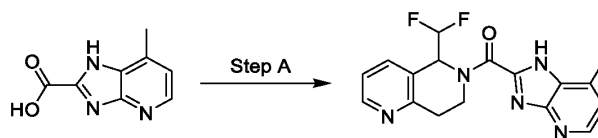
[00799] Step A: To a solution of tert-butyl 4-chloro-5-methyl-7,8-dihydro-5H-1,6-naphthyridine-6-carboxylate (50.0 mg, 0.177 mmol) in EtOAc (2.00 mL) was added HCl/EtOAc (4 M, 5.00 mL). The resulting mixture was stirred at 20 °C for 1 h. The mixture was concentrated under reduced pressure to give 4-chloro-5-methyl-5,6,7,8-tetrahydro-1,6-naphthyridine. ¹H NMR (400 MHz, DMSO-*d*₆) δ 9.85 – 9.46 (m, 2H), 8.48 (d, *J* = 5.3 Hz, 1H), 7.53 (d, *J* = 5.4 Hz, 1H), 4.81 (br d, *J* = 6.3 Hz, 1H), 3.68 – 3.44 (m, 2H), 3.26 – 3.05 (m, 2H), 1.59 (d, *J* = 6.9 Hz, 3H).

[00800] Step B: To a solution of 4-chloro-5-methyl-5,6,7,8-tetrahydro-1,6-naphthyridine (20.0 mg, 0.091 mmol) in THF (1.00 mL) was added 7-chloro-4-fluoro-1H-benzo[d]imidazole-2-carboxylic acid (19.6 mg, 0.091 mmol), DIEA (29.5 mg, 0.228 mmol) and BOP-Cl (25.6 mg, 0.100 mmol) the mixture was stirred at 20 °C for 1 h. The reaction mixture was added to H₂O (2.00 mL) and extracted with EtOAc (3.00 mL x 3). The combined organic layers were dried over Na₂SO₄, filtered and concentrated under reduced pressure to give a residue which was purified by preparative TLC (pure EtOAc) to give (7-chloro-4-fluoro-1H-benzo[d]imidazol-2-yl)(4-chloro-5-methyl-7,8-dihydro-1,6-naphthyridin-6(5H)-yl)methanone. LC-MS: 379.1 [M+H]⁺.

[00801] Step C: (7-Chloro-4-fluoro-1H-benzo[d]imidazol-2-yl)(4-chloro-5-methyl-7,8-dihydro-1,6-naphthyridin-6(5H)-yl)methanone (25.0 mg, 0.066 mmol) was further separated by SFC separation DAICEL CHIRALPAK IG (250 × 30 mm, 10 μm); flow rate: 30 mL/min; gradient: 40% B over 14 min; mobile phase A: heptane, mobile phase B: CO₂ – IPA (0.1% NH₃H₂O). First eluted compound: LC-MS: 379.0 [M+H]⁺. ¹H NMR (400 MHz, DMSO-*d*₆) δ 14.35 – 13.92 (m, 1H), 8.48 – 8.31 (m, 1H), 7.53 – 7.38 (m, 1H), 7.34 – 6.99 (m, 2H), 6.03 – 4.88 (m, 1H), 4.77 – 3.77 (m, 1H), 3.68 – 3.37 (m, 1H), 3.24 – 2.95 (m, 2H), 1.70 – 1.50 (m, 3H). Second eluted compound: LC-MS: 379.0 [M+H]⁺. ¹H NMR (400 MHz, DMSO-*d*₆) δ 14.34 – 13.86 (m, 1H), 8.48 – 8.31 (m, 1H), 7.54 – 7.35 (m, 1H), 7.31 – 7.01 (m, 2H), 5.99 – 4.85 (m,

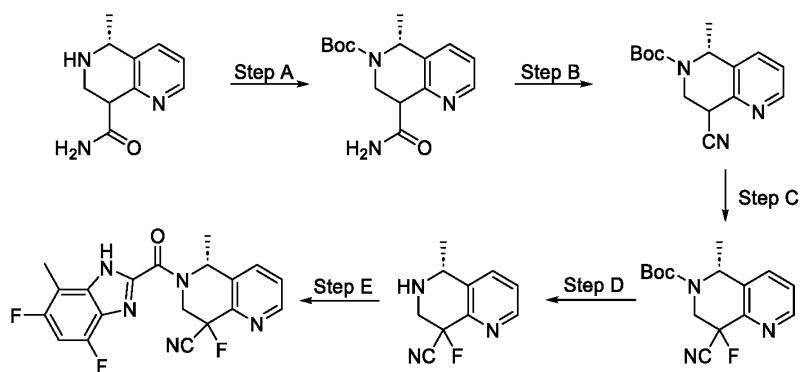
1H), 4.77 – 3.78 (m, 1H), 3.65 – 3.36 (m, 1H), 3.27 – 2.98 (m, 2H), 1.72 – 1.43 (m, 3H). The absolute stereochemistry for the first and second eluted compounds was not determined.

Example 214: (5-(Difluoromethyl)-7,8-dihydro-1,6-naphthyridin-6(5H)-yl)(7-methyl-1H-imidazo[4,5-b]pyridin-2-yl)methanone



[00802] Step A: To a solution of (5S)-5-(difluoromethyl)-5,6,7,8-tetrahydro-1,6-naphthyridine (62.3 mg, 0.282 mmol, HCl Salt) in THF (5.00 mL) was added 7-methyl-1H-imidazo[4,5-b]pyridine-2-carboxylic acid (50.0 mg, 0.282 mmol), DIEA (91.2 mg, 0.706 mmol) and BOP-Cl (79.0 mg, 0.310 mmol). The mixture was stirred at 20 °C for 12 h. The reaction mixture was poured into H₂O (2.00 mL) and extracted with EtOAc (5.00 mL x 3). The combined organic layers were dried over Na₂SO₄, filtered and concentrated under reduced pressure to give a residue which was purified by preparative HPLC (Phenomenex Luna C18 column (100 × 40 mm, 5 μm); flow rate: 25 mL/min; gradient: 1% – 20% B over 8 min; mobile phase A: 0.04% aqueous HCl, mobile phase B: acetonitrile) to give (5-(difluoromethyl)-7,8-dihydro-1,6-naphthyridin-6(5H)-yl)(7-methyl-1H-imidazo[4,5-b]pyridin-2-yl)methanone. LC-MS: 344.1 [M+H]⁺. ¹H NMR (400 MHz, DMSO-d₆) δ 8.93 - 8.29 (m, 4H), 7.98 - 7.73 (m, 1H), 7.63 - 7.33 (m, 1H), 6.92 - 6.49 (m, 1H), 6.42 - 5.32 (m, 1H), 5.01 - 3.79 (m, 1H), 3.59 - 3.15 (m, 3H), 2.83 - 2.63 (m, 3H).

Example 215: (5R)-6-(4,6-Difluoro-7-methyl-1H-benzo[d]imidazole-2-carbonyl)-8-fluoro-5-methyl-5,6,7,8-tetrahydro-1,6-naphthyridine-8-carbonitrile



[00803] Step A: A mixture of (5R)-5-methyl-5,6,7,8-tetrahydro-1,6-naphthyridine-8-carboxamide (500 mg, 2.61 mmol), Boc₂O (856 mg, 3.92 mmol) and TEA (794 mg, 7.84 mmol) in DCM (10 mL) was stirred at 20 °C for 12 h. The reaction mixture was poured into water (10 mL) and extracted with EtOAc (10 mL x 3). The combined organic phase was washed with brine

(10 mL), dried over anhydrous Na_2SO_4 , filtered and concentrated in vacuum to give a residue which was purified by prep-HPLC (Phenomenex luna C18 (250 x 70 mm, 15 μm), Flow rate: 130 ml/min; gradient: 7%-37% B over 8 min; mobile phase A: water (0.04% HCl), mobile phase B: acetonitrile) to give tert-butyl (5R)-8-carbamoyl-5-methyl-7,8-dihydro-1,6-naphthyridine-6(5H)-carboxylate. LC-MS: 292.4 $[\text{M}+\text{H}]^+$.

[00804] Step B: To a solution of tert-butyl (5R)-8-carbamoyl-5-methyl-7,8-dihydro-1,6-naphthyridine-6(5H)-carboxylate (220 mg, 0.755 mmol) in THF (5.0 mL) was added BURGESS REAGENT (540 mg, 2.27 mmol). The mixture was stirred at 20 °C for 1 h. The reaction mixture was concentrated to give a residue which was diluted with H_2O (10 mL) and extracted with EtOAc (3 mL $\times$ 3). The combined organic layers were dried over Na_2SO_4 , filtered and the filtrate was concentrated to give a residue which was purified by flash silica gel chromatography using a gradient of Petroleum ether/EtOAc from 0/1 to 1/1 to give tert-butyl (5R)-8-cyano-5-methyl-7,8-dihydro-1,6-naphthyridine-6(5H)-carboxylate. LC-MS: 273.9 $[\text{M}+\text{H}]^+$.

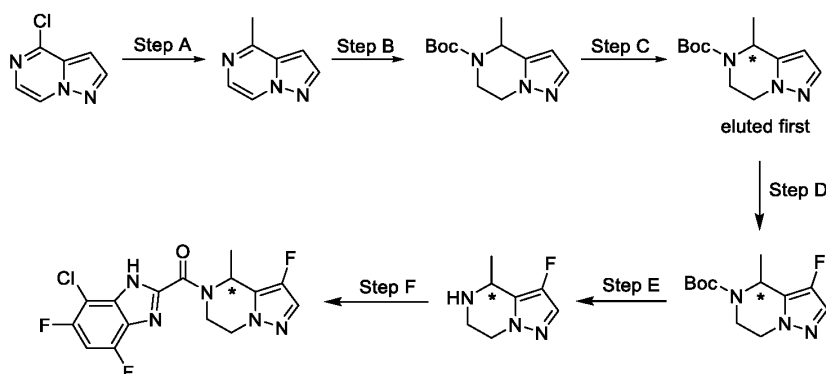
[00805] Step C: To a solution of tert-butyl (5R)-8-cyano-5-methyl-7,8-dihydro-1,6-naphthyridine-6(5H)-carboxylate (80 mg, 0.292 mmol) and NFSI (73.84 mg, 0.234 mmol) in THF (5 mL) was added DBU (53.47 mg, 0.351 mmol). The mixture was stirred at 20 °C for 2 h. The reaction mixture was filtered and the filtrate was concentrated in vacuum. The residue was purified by flash silica gel chromatography using a gradient of Petroleum ether/Ethyl acetate from 0/1 to 1/1 to give tert-butyl (5R)-8-cyano-8-fluoro-5-methyl-7,8-dihydro-1,6-naphthyridine-6(5H)-carboxylate. LC-MS: 292.4 $[\text{M}+\text{H}]^+$. ^1H NMR (400 MHz, CDCl_3) δ = 8.72 - 8.67 (m, 1H), 7.64 - 7.57 (m, 1H), 7.48 - 7.39 (m, 1H), 5.59 - 5.35 (m, 1H), 5.05 - 4.84 (m, 1H), 3.79 - 3.52 (m, 1H), 1.55 (s, 9H), 1.52 (d, J = 2.0 Hz, 3H).

[00806] Step D: To a solution of tert-butyl (5R)-8-cyano-8-fluoro-5-methyl-5,7-dihydro-1,6-naphthyridine-6-carboxylate (40.0 mg, 0.137 mmol) in DCM (2.0 mL) was added TFA (783 mg, 6.87 mmol). The mixture was stirred at 20 °C for 30 min. The reaction mixture was concentrated to give (5R)-8-fluoro-5-methyl-5,6,7,8-tetrahydro-1,6-naphthyridine-8-carbonitrile (TFA salt).

[00807] Step E: To a solution of (5R)-8-fluoro-5-methyl-6,7-dihydro-5H-1,6-naphthyridine-8-carbonitrile (40 mg, 0.131 mmol, TFA salt) and 4,6-difluoro-7-methyl-1H-benzimidazole-2-carboxylic acid (27.80 mg, 0.131 mmol) in THF (2.0 mL) was added BOP-Cl (66.72 mg, 0.262 mmol) and DIEA (33.87 mg, 0.262 mmol). The mixture was stirred at 20 °C for 30 min. The reaction mixture was filtered and the filtrate was concentrated in vacuum to give a residue which was purified by prep-HPLC (WePure Biotech XP tC18 (150*40*7 μm), Flow rate: 50.00ml/min, Gradient: B from 35.00% to 65.00% in 8.00min, Mobile phase: A: H_2O (10mM NH_4HCO_3);B: ACN) to give (5R)-6-(4,6-difluoro-7-methyl-1H-benzo[d]imidazole-2-carbonyl)-8-fluoro-5-

methyl-5,6,7,8-tetrahydro-1,6-naphthyridine-8-carbonitrile. LC-MS: 386.1 $[M+H]^+$. 1H NMR (400 MHz, DMSO- d_6) δ 14.27 - 13.66 (m, 1H), 8.75 - 8.66 (m, 1H), 8.15 - 7.98 (m, 1H), 7.72 - 7.57 (m, 1H), 7.27 - 7.13 (m, 1H), 6.96 - 6.49 (m, 1H), 5.94 - 5.42 (m, 1H), 4.38 - 4.01 (m, 1H), 2.44 (br d, J = 11.5 Hz, 3H), 1.88 - 1.60 (m, 3H).

Example 216A: (R) or (S)-(7-Chloro-4,6-difluoro-1H-benzo[d]imidazol-2-yl)(3-fluoro-4-methyl-6,7-dihydropyrazolo[1,5-a]pyrazin-5(4H)-yl)methanone



[00808] Step A: To a solution of 4-chloropyrazolo[1,5-a]pyrazine (180 g, 1170 mmol) in dioxane (1.80 L) and H₂O (180 mL) was added 2,4,6-trimethyl-1,3,5,2,4,6-trioxatriborinane (3.5 M, 502 mL) and Cs₂CO₃ (573 g, 1758 mmol). The suspension was bubbled with N₂ for 2 minutes, then Pd(dppf)Cl₂ (42.9 g, 85.6 mmol) was added. The mixture was stirred at 100 °C for 14 h. The reaction mixture was poured into H₂O (1.5 L) at 25 °C, and then extracted with EtOAc (1.50 L x 3). The combined organic layers dried over Na₂SO₄, filtered and concentrated under reduced pressure to give a residue which was purified by flash silica gel chromatography using a gradient of EtOAc/petroleum ether from 0/1 to 1/3 to give 4-methylpyrazolo[1,5-a]pyrazine. LC-MS: 134.2 $[M+H]^+$. 1H NMR (400 MHz, DMSO- d_6) δ 8.60 (d, J = 4.8 Hz, 1H), 8.11 (d, J = 2.3 Hz, 1H), 7.74 (d, J = 4.9 Hz, 1H), 7.01 (d, J = 2.1 Hz, 1H), 1.99 (s, 3H).

[00809] Step B: Solution 1: 4-methylpyrazolo[1,5-a]pyrazine (125 g, 939 mmol) and Boc₂O (204 g, 939 mmol) in THF (3.75 L). The fixed bed (named FLR1, volume 50 mL) was completely packed with granular catalyst 5% Pd/C (1.00 eq)(WXC1032). The H₂ back pressure regulator was adjusted to 1 MPa, and the flow rate of H₂ was 150 mL/min. Then the solution S1 was pumped by Pump 1 {S1, P1, 2.2 mL/min} to fixed bed {FLR1, SS, fixed bed, 6.350(1/4'')mm, 10 mL, 80 °C}. The solution S1 was flowing through {FLR1, 4.54 min} to leave the reactor zone, then the reaction mixture was collected from the reactor output. The mixture was concentrated under vacuum to give a residue to give tert-butyl 4-methyl-6,7-dihydropyrazolo[1,5-a]pyrazine-5(4H)-carboxylate. LC-MS: 238.2 $[M+H]^+$. 1H NMR (400 MHz, DMSO- d_6) δ 7.40 (d, J = 1.5 Hz, 1H), 6.14 (s, 1H), 5.23 (br d, J = 6.3 Hz, 1H), 4.31 - 4.10 (m,

2H), 3.94 (dt, $J = 4.3, 12.2$ Hz, 1H), 3.38 (br d, $J = 10.8$ Hz, 1H), 1.44 (s, 9H), 1.37 (d, $J = 6.6$ Hz, 3H).

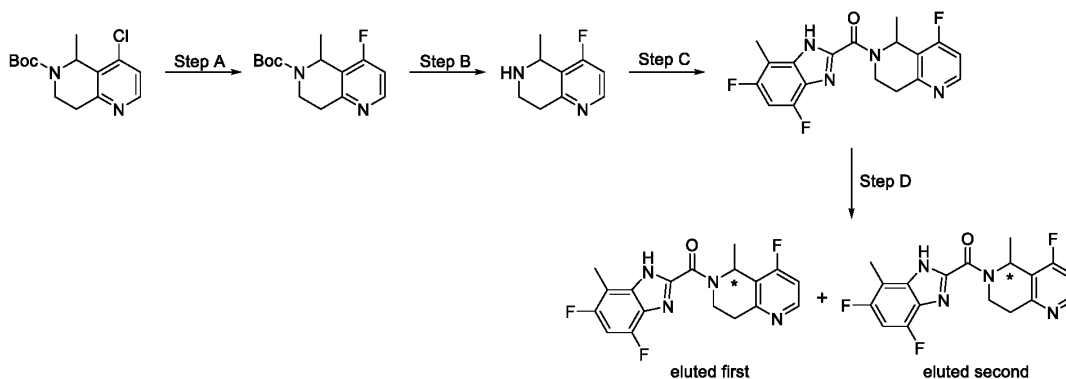
[00810] Step C: tert-Butyl 4-methyl-6,7-dihydropyrazolo[1,5-a]pyrazine-5(4H)-carboxylate (70.0 g, 295 mmol), was further separated by SFC separation DAICEL CHIRALPAK IG (250 × 50 mm, 10 μm); flow rate: 30 mL/min; gradient: 15% B over 14 min; mobile phase A: heptane, mobile phase B: CO₂ – EtOH (0.1% NH₃H₂O) tert-butyl 4-methyl-6,7-dihydropyrazolo[1,5-a]pyrazine-5(4H)-carboxylate (first eluting isomer). First eluted compound: LC-MS: 238.3 [M+H]⁺. ¹H NMR (400 MHz, DMSO-*d*₆) δ 7.40 (d, $J = 1.8$ Hz, 1H), 6.15 (d, $J = 1.1$ Hz, 1H), 5.23 (br d, $J = 6.4$ Hz, 1H), 4.27 – 4.11 (m, 2H), 3.94 (dt, $J = 4.4, 12.2$ Hz, 1H), 3.42 – 3.33 (m, 1H), 1.44 (s, 9H), 1.37 (d, $J = 6.8$ Hz, 3H).

[00811] Step D: To a solution of tert-butyl 4-methyl-6,7-dihydropyrazolo[1,5-a]pyrazine-5(4H)-carboxylate (180 mg, 0.758 mmol) in DCM (5.0 mL) was added 1-(chloromethyl)-4-fluoro-1,4-diazoniabicyclo[2.2.2]octane;ditetrafluoroborate (537 mg, 1.52 mmol). The mixture was stirred at 20 °C for 16 h. The reaction mixture was filtered and the filtrate was concentrated to give a residue which was purified by preparative TLC (SiO₂, Petroleum ether/EtOAc=3/1) to give tert-butyl 3-fluoro-4-methyl-6,7-dihydropyrazolo[1,5-a]pyrazine-5(4H)-carboxylate. LC-MS: 256.2 [M+H]⁺. ¹H NMR (400 MHz, DMSO-*d*₆) δ 7.48 (d, $J = 4.3$ Hz, 1H), 5.24 (br d, $J = 5.5$ Hz, 1H), 4.28 - 4.17 (m, 1H), 4.13 - 4.04 (m, 1H), 3.90 (dt, $J = 4.3, 12.2$ Hz, 1H), 3.48 - 3.36 (m, 1H), 1.44 (s, 9H), 1.38 - 1.36 (m, 3H).

[00812] Step E: tert-Butyl 3-fluoro-4-methyl-6,7-dihydropyrazolo[1,5-a]pyrazine-5(4H)-carboxylate (50 mg, 0.195 mmol) was dissolved in HCl/EtOAc (4 M, 2 mL). The mixture was stirred at 20 °C for 1 h. The reaction mixture was concentrated to give 3-fluoro-4-methyl-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrazine (HCl). LC-MS: 156.2 [M+H]⁺.

[00813] Step F: To a solution of 3-fluoro-4-methyl-4,5,6,7-tetrahydropyrazolo[1,5-a]pyrazine (50.0 mg, 0.260 mmol, HCl salt) and 7-chloro-4,6-difluoro-1H-benzimidazole-2-carboxylic acid (60.7 mg, 0.260 mmol) in THF (2.00 mL) was added BOP-Cl (133 mg, 0.521 mmol) and DIEA (67.4 mg, 0.521 mmol). The mixture was stirred at 20 °C for 1 h. The reaction mixture was filtered and the filtrate was concentrated in vacuum to give a residue which was purified by preparative TLC (SiO₂, DCM/MeOH=20/1) to give (7-chloro-4,6-difluoro-1H-benzo[d]imidazol-2-yl)(3-fluoro-4-methyl-6,7-dihydropyrazolo[1,5-a]pyrazin-5(4H)-yl)methanone. LC-MS: 370.0 [M+H]⁺. ¹H NMR (400 MHz, DMSO-*d*₆) δ 7.65 - 7.39 (m, 1H), 7.27 (br t, $J = 10.0$ Hz, 1H), 6.45 - 5.75 (m, 1H), 5.43 - 4.79 (m, 1H), 4.25 - 3.96 (m, 2H), 3.84 - 3.74 (m, 1H), 1.68 - 1.10 (m, 3H). The absolute stereochemistry for Example 216A was not determined.

Examples 217A and 217B: (R) or (S)-(4,6-Difluoro-7-methyl-1H-benzo[d]imidazol-2-yl)(4-fluoro-5-methyl-7,8-dihydro-1,6-naphthyridin-6(5H)-yl)methanone and (R) or (S)-(4,6-Difluoro-7-methyl-1H-benzo[d]imidazol-2-yl)(4-fluoro-5-methyl-7,8-dihydro-1,6-naphthyridin-6(5H)-yl)methanone



[00814] Step A: To a solution of tert-butyl 4-chloro-5-methyl-7,8-dihydro-1,6-naphthyridine-6(5H)-carboxylate (200 mg, 0.707 mmol) in DMSO (16.0 mL) was added 18-crown-6 (37.4 mg, 0.141 mmol), TBAC (39.3 mg, 0.141 mmol) and CsF (1.07 g, 7.07 mmol) at 20 °C under nitrogen. The mixture was stirred at 140 °C for 12 h. The combined mixture was poured into H₂O (30.0 mL) and extracted with EtOAc (15.0 mL x 3). The combined organic layers were dried over Na₂SO₄, filtered and concentrated under vacuum to give a residue which was purified by preparative TLC (petroleum ether: EtOAc=1:1, *R_f*= 0.43) to give tert-butyl 4-fluoro-5-methyl-7,8-dihydro-1,6-naphthyridine-6(5H)-carboxylate. LC-MS: 267.2 [M+H]⁺. ¹H NMR (400 MHz, CDCl₃) δ 8.41 (br s, 1H), 6.89 (dd, *J* = 5.5, 9.4 Hz, 1H), 5.66 – 5.25 (m, 1H), 4.45 – 4.17 (m, 1H), 3.41 – 3.16 (m, 1H), 3.12 – 2.89 (m, 2H), 1.51 (s, 9H), 1.46 (d, *J* = 6.6 Hz, 3H).

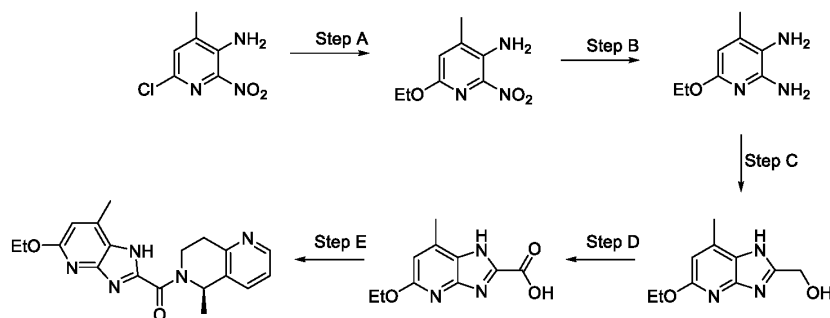
[00815] Step B: To a solution of tert-butyl 4-fluoro-5-methyl-7,8-dihydro-1,6-naphthyridine-6(5H)-carboxylate (25.0 mg, 0.094 mmol) in EtOAc (0.100 mL) was added HCl/EtOAc (4 M, 4.00 mL) at 20 °C. The mixture was stirred at 20 °C for 4 h. The mixture was concentrated under vacuum at 20 °C to give 4-fluoro-5-methyl-5,6,7,8-tetrahydro-1,6-naphthyridine. LC-MS: 167.2 [M+H]⁺.

[00816] Step C: To a solution of 4-fluoro-5-methyl-5,6,7,8-tetrahydro-1,6-naphthyridine (19.1 mg, 0.094 mmol) in DMF (0.500 mL) was added 4,6-difluoro-7-methyl-1H-benzo[d]imidazole-2-carboxylic acid (20.0 mg, 0.094 mmol), DIEA (24.4 mg, 0.189 mmol) and HATU (35.8 mg, 0.094 mmol), the mixture was stirred at 20 °C for 1 h. The reaction mixture was poured into H₂O (5.00 mL) and extracted with EtOAc (5.00 mL x 3). The combined organic layers were dried over Na₂SO₄, filtered and concentrated under reduced pressure to give a residue, which was purified by preparative TLC (EtOAc) to give (4,6-difluoro-7-methyl-1H-benzo[d]imidazol-2-

yl)(4-fluoro-5-methyl-7,8-dihydro-1,6-naphthyridin-6(5H)-yl)methanone. LC-MS: 361.2 [M+H]⁺.

[00817] Step D: (4,6-Difluoro-7-methyl-1H-benzo[d]imidazol-2-yl)(4-fluoro-5-methyl-7,8-dihydro-1,6-naphthyridin-6(5H)-yl)methanone (12.0 mg) was further separated by SFC separation column: DAICEL CHIRALPAK IG (250mm x 30mm, 10μm); mobile phase: [CO₂-MeOH (0.1% NH₃H₂O)]; B%: 40%, isocratic elution mode. First eluted compound: LC-MS: 361.1 [M+H]⁺. ¹H NMR (400 MHz, DMSO-d₆) δ 14.04 – 13.44 (m, 1H), 8.47 (ddd, *J* = 5.6, 8.3, 13.6 Hz, 1H), 7.38 – 6.59 (m, 2H), 5.93 – 5.17 (m, 1H), 4.82 – 3.66 (m, 1H), 3.24 – 2.92 (m, 3H), 2.45 – 2.38 (m, 3H), 1.76 – 1.47 (m, 3H). Second eluted compound: LC-MS: 361.1 [M+H]⁺. ¹H NMR (400 MHz, DMSO-d₆) δ 13.95 – 13.54 (m, 1H), 8.47 (ddd, *J* = 5.6, 8.3, 13.6 Hz, 1H), 7.35 – 6.61 (m, 2H), 6.03 – 5.33 (m, 1H), 4.88 – 3.42 (m, 1H), 3.29 – 2.93 (m, 3H), 2.42 (br s, 3H), 1.81 – 1.40 (m, 3H). The absolute stereochemistry for the first and second eluted compounds was not determined.

Example 218: (R)-(5-Ethoxy-7-methyl-1H-imidazo[4,5-b]pyridin-2-yl)(5-methyl-7,8-dihydro-1,6-naphthyridin-6(5H)-yl)methanone



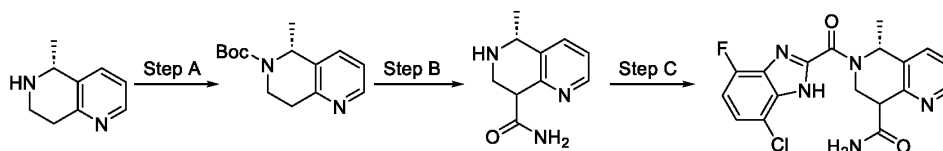
[00818] Step A: To a stirred solution of 6-chloro-4-methyl-2-nitropyridin-3-amine (2.00 g, 10.7 mmol) in EtOH (2.00 mL) was added EtONa (3.63 g, 10.7 mmol, 20% purity). The mixture was stirred at 145 °C for 1 h. The reaction mixture was diluted with H₂O (50.00 mL) and extracted with EtOAc (50.00 mL x 4). The combined organic layers were washed with brine (35 mL x 1), dried over Na₂SO₄, filtered and concentrated under reduced pressure to give a residue which was purified by flash silica gel chromatography using a gradient of EtOAc/petroleum ether from 0% to 7% to give 6-ethoxy-4-methyl-2-nitropyridin-3-amine. LC-MS: 198.2 [M+H]⁺. ¹H NMR (400 MHz, CDCl₃) δ 6.85 - 6.55 (m, 2H), 5.98 (d, *J* = 0.8 Hz, 1H), 4.33 (q, *J* = 7.2 Hz, 2H), 2.57 (d, *J* = 0.6 Hz, 3H), 1.37 (t, *J* = 7.1 Hz, 3H).

[00819] Step B: 6-Ethoxy-4-methyl-2-nitro-pyridin-3-amine (2.50 g, 12.7 mmol) in THF (100 mL) was stirred at 15 °C until becoming a clear solution. The fixed bed SS, 5.00 mL with granular catalyst 1%Pt/SX-C (1.00 eq) was heated to 40 °C. The H₂ back pressure regulator was

adjusted to 0.5 MPa. The above solution was pumped into the fixed bed at a flow rate of 0.3 mL/min, and the flow rate of H₂ was 30 mL/min. The reaction mixture was collected after running 30 min. The fixed bed was washed by extra MeOH (500 mL). The reaction mixture was concentrated under reduced pressure to remove solvent to give 6-ethoxy-4-methylpyridine-2,3-diamine. LC-MS: 168.2 [M+H]⁺.

[00820] Steps C, D, and E: The title compound was prepared from 6-ethoxy-4-methylpyridine-2,3-diamine according to the procedure of Example 21, Steps A, B, and C. LC-MS: 352.2 [M+H]⁺. ¹H NMR (400 MHz, DMSO-*d*₆) δ 13.44 (br s, 1H), 8.44 – 8.38 (m, 1H), 7.79 (d, *J* = 7.5 Hz, 1H), 7.31 – 7.22 (m, 1H), 6.62 (s, 1H), 5.75 – 5.51 (m, 1H), 4.34 (br d, *J* = 7.1 Hz, 1H), 4.39 – 4.29 (m, 1H), 3.74 – 3.58 (m, 1H), 3.24 – 3.11 (m, 1H), 2.98 (br d, *J* = 9.0 Hz, 1H), 2.58 – 2.52 (m, 3H), 1.55 (d, *J* = 6.8 Hz, 3H), 1.34 (t, *J* = 7.1 Hz, 3H).

Example 219: (5R)-6-(7-Chloro-4-fluoro-1H-benzo[d]imidazole-2-carbonyl)-5-methyl-5,6,7,8-tetrahydro-1,6-naphthyridine-8-carboxamide



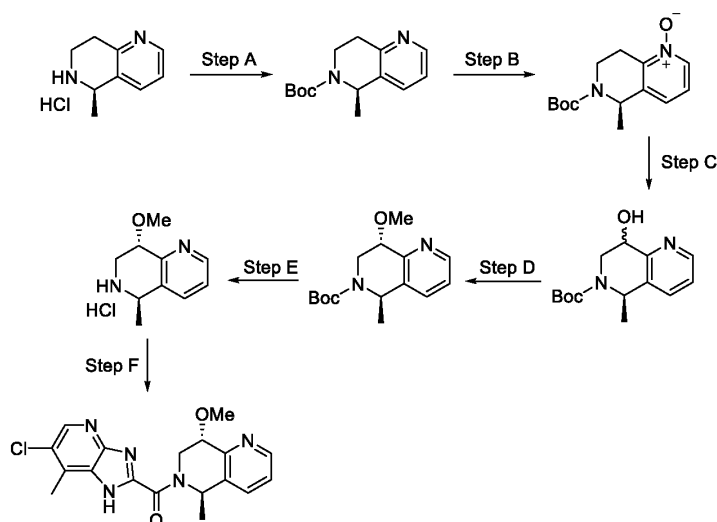
[00821] Step A: To a solution of (5R)-5-methyl-5,6,7,8-tetrahydro-1,6-naphthyridine (5.00 g, 27.1 mmol, HCl) in DCM (100 mL) were added TEA (5.48 g, 54.2 mmol) and Boc₂O (7.09 g, 32.5 mmol) at 20 °C and the mixture was stirred at 20 °C for 1 h. The reaction mixture was concentrated in vacuum to give a residue which was purified by flash silica gel chromatography using a gradient of EtOAc/petroleum ether from 0/1 to 1/1 to give tert-butyl (R)-5-methyl-7,8-dihydro-1,6-naphthyridine-6(5H)-carboxylate. LC-MS: 248.9 [M+H]⁺.

[00822] Step B: To a solution of tert-butyl (R)-5-methyl-7,8-dihydro-1,6-naphthyridine-6(5H)-carboxylate (100 mg, 0.402 mmol) in Hexane (2.00 mL) was added n-BuLi (2.5 M, 242 μ L) at 0 °C and then the reaction mixture was stirred at 0 °C for 1 h. Then isocyanato(trimethyl)silane (162 mg, 1.41 mmol) was added dropwise at -20 °C and the mixture was stirred at -20 °C for 2 h. The reaction mixture was diluted with H₂O (2.00 mL) and adjusted to pH 2 by addition of conc. HCl. The aqueous solution was concentrated in vacuo to give (5R)-5-methyl-5,6,7,8-tetrahydro-1,6-naphthyridine-8-carboxamide (HCl). LC-MS: 192.5 [M+H]⁺.

[00823] Step C: To a solution of (5R)-5-methyl-5,6,7,8-tetrahydro-1,6-naphthyridine-8-carboxamide (100 mg, 0.439 mmol, HCl) and 7-chloro-4-fluoro-1H-benzimidazole-2-carboxylic acid (94.2 mg, 0.439 mmol) in THF (2.00 mL) was added BOP-Cl (224 mg, 0.878 mmol) and DIEA (114 mg, 0.878 mmol). The mixture was stirred at 20 °C for 1 h. The reaction mixture was

concentrated to give a residue. The residue was diluted with H₂O (10.0 mL) and extracted with EtOAc (3.00 mL × 3). The combined organic layers were dried over Na₂SO₄, filtered and the filtrate was concentrated to give a residue which was purified by flash silica gel chromatography using a gradient of MeOH/DCM from 0/1 to 1/1 to give (5R)-6-(7-chloro-4-fluoro-1H-benzo[d]imidazole-2-carbonyl)-5-methyl-5,6,7,8-tetrahydro-1,6-naphthyridine-8-carboxamide. LC-MS: 388.1 [M+H]⁺. ¹H NMR (400 MHz, CDCl₃) δ 12.65 - 12.15 (m, 1H), 8.58 - 8.47 (m, 1H), 7.68 - 7.60 (m, 1H), 7.34 (dd, *J* = 4.8, 7.8 Hz, 1H), 7.17 (td, *J* = 4.3, 8.6 Hz, 1H), 7.03 - 6.90 (m, 1H), 5.91 - 5.80 (m, 1H), 5.75 - 5.59 (m, 1H), 3.90 (br d, *J* = 3.0 Hz, 1H), 3.74 (dd, *J* = 3.8, 14.3 Hz, 1H), 1.64 (d, *J* = 6.9 Hz, 3H).

Example 220: 6-Chloro-7-methyl-1H-imidazo[4,5-b]pyridin-2-yl)((5R,8S)-8-methoxy-5-methyl-7,8-dihydro-1,6-naphthyridin-6(5H)-yl)methanone



[00824] Step A: To a solution of (R)-5-methyl-5,6,7,8-tetrahydro-1,6-naphthyridine (30.0 g, 162 mmol, HCl) in DCM (300 mL) was added (Boc)₂O (42.5 g, 195 mmol) and TEA (32.9 g, 325 mmol, 45.2 mL). The mixture was stirred at 20 °C for 2 h. The reaction mixture was poured into H₂O (200 mL) and extracted with DCM (200 mL × 3). The combined organic layers were dried over Na₂SO₄, filtered, and concentrated under vacuum to give a residue, which was purified by flash silica gel chromatography using a gradient of EtOAc/petroleum ether from 0/1 to 1/1 to give tert-butyl (R)-5-methyl-7,8-dihydro-1,6-naphthyridine-6(5H)-carboxylate. LC-MS: 249.3 [M+H]⁺. ¹H NMR (400 MHz, DMSO-*d*₆) δ 8.40 - 8.34 (m, 1H), 7.66 (d, *J* = 7.6 Hz, 1H), 7.22 (dd, *J* = 4.8, 7.9 Hz, 1H), 5.13 (br dd, *J* = 2.3, 4.3 Hz, 1H), 4.24 - 4.02 (m, 1H), 3.28 - 3.13 (m, 1H), 2.95 - 2.76 (m, 2H), 1.48 - 1.33 (m, 12H).

[00825] Steps B and C: (5R)-tert-Butyl 8-hydroxy-5-methyl-7,8-dihydro-1,6-naphthyridine-6(5H)-carboxylate was prepared according to the procedure of Example 74A and 74B, Steps A

and B. LC-MS: 264.9 [M+H]⁺. ¹H NMR (400 MHz, DMSO-*d*₆) δ 8.45 (d, *J* = 4.0 Hz, 1H), 7.71 (d, *J* = 7.5 Hz, 1H), 7.31 (dd, *J* = 4.6, 7.9 Hz, 1H), 5.37 – 5.06 (m, 2H), 4.49 (br s, 1H), 4.27 – 4.08 (m, 1H), 3.25 – 3.13 (m, 1H), 1.54 – 1.26 (m, 12H).

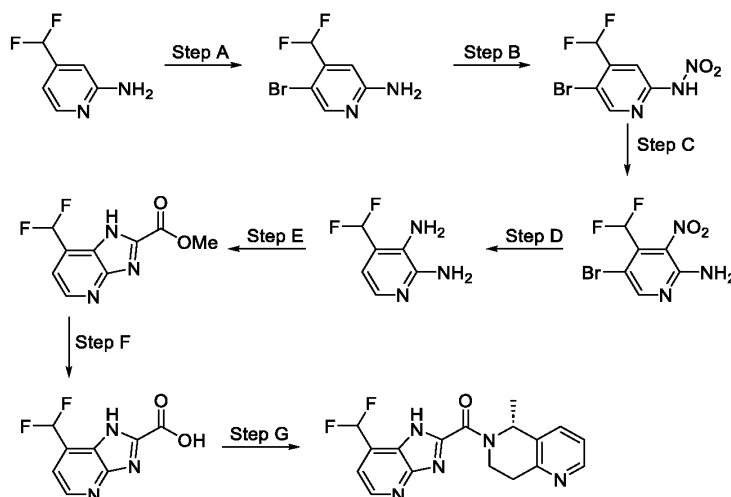
[00826] Step D: To a solution of (5R)-tert-butyl 8-hydroxy-5-methyl-7,8-dihydro-1,6-naphthyridine-6(5H)-carboxylate (30.0 g, 114 mmol, mixture of diastereoisomers) in THF (300 mL) was added t-BuONa (32.7 g, 341 mmol) and MeI (32.2 g, 227 mmol) at 0 °C under a nitrogen atmosphere. The mixture was stirred at 25 °C for 3 h under a nitrogen atmosphere. The mixture was diluted with H₂O (600 mL) and extracted with DCM (400 mL x 5). The combined organic layers were dried over Na₂SO₄, filtered and concentrated under reduced pressure to give a residue, which was purified by preparative HPLC (Phenomenex Gemini C18 column (250 × 100 mm, 10 μm); flow rate: 280 mL/min; gradient: 25% – 55% B over 8 min; mobile phase A: H₂O (10 mM NH₄HCO₃), mobile phase B: acetonitrile to give tert-butyl (5R,8S)-8-methoxy-5-methyl-7,8-dihydro-5H-1,6-naphthyridine-6-carboxylate. ¹H NMR (400 MHz, DMSO-*d*₆) δ 8.46 (br d, *J* = 3.1 Hz, 1H), 7.75 (br d, *J* = 7.6 Hz, 1H), 7.36 (dd, *J* = 4.7, 7.8 Hz, 1H), 5.34 – 5.03 (m, 1H), 4.51 – 4.33 (m, 1H), 4.28 – 4.02 (m, 1H), 3.45 – 3.34 (m, 3H), 3.28 – 3.08 (m, 1H), 1.49 – 1.24 (m, 12H).

[00827] Step E: To a solution of tert-butyl (5R,8S)-8-methoxy-5-methyl-7,8-dihydro-1,6-naphthyridine-6(5H)-carboxylate (3.00 g, 10.8 mmol) in EtOAc (60.0 mL) was added HCl/EtOAc (4 M, 300 mL), the mixture was stirred at 25 °C for 12 h. The mixture was concentrated under reduced pressure to give (5R,8S)-8-methoxy-5-methyl-5,6,7,8-tetrahydro-1,6-naphthyridine. LC-MS: 179.2 [M+H]⁺. ¹H NMR (400 MHz, DMSO-*d*₆) δ 10.13 – 9.95 (m, 1H), 9.44 (br d, *J* = 4.9 Hz, 1H), 8.72 – 8.57 (m, 1H), 7.90 (d, *J* = 8.0 Hz, 1H), 7.54 (dd, *J* = 4.9, 7.9 Hz, 1H), 4.77 – 4.64 (m, 1H), 4.52 (t, *J* = 2.9 Hz, 1H), 3.73 – 3.51 (m, 2H), 1.59 (d, *J* = 7.0 Hz, 3H).

[00828] Step F: To a solution of 6-chloro-7-methyl-1H-imidazo[4,5-*b*]pyridine-2-carboxylic acid (50.0 mg, 0.236 mmol) and (5R,8S)-8-methoxy-5-methyl-5,6,7,8-tetrahydro-1,6-naphthyridine (50.7 mg, 0.236 mmol, HCl) in THF (5.00 mL) was added BOP-Cl (66.2 mg, 0.260 mmol) and DIEA (76.4 mg, 0.591 mmol), then the mixture was stirred at 20 °C for 5 h. The reaction mixture was poured into H₂O (5.00 mL) and extracted with DCM (5.00 mL x 3). The combined organic layers were dried over Na₂SO₄, filtered, and concentrated under vacuum to give a residue, which was purified by preparative HPLC column: Phenomenex luna C18 100 x 40mm x 5 μm; mobile phase: [H₂O(0.04% HCl)-ACN]; gradient: 10%-40% B over 8.0 min) to give (6-chloro-7-methyl-1H-imidazo[4,5-*b*]pyridin-2-yl)((5R,8S)-8-methoxy-5-methyl-7,8-dihydro-1,6-naphthyridin-6(5H)-yl)methanone. LC-MS: 372.1 [M+H]⁺. ¹H NMR (400 MHz,

DMSO-*d*₆) δ 8.72 (br d, *J* = 3.3 Hz, 1H), 8.52 – 8.40 (m, 1H), 8.37 – 8.21 (m, 1H), 7.85 – 7.69 (m, 1H), 6.69 – 6.05 (m, 1H), 6.04 – 5.07 (m, 1H), 4.66 – 4.37 (m, 1H), 3.82 (br d, *J* = 13.6 Hz, 1H), 3.47 (br s, 1H), 3.22 (s, 2H), 2.71 – 2.58 (m, 3H), 1.78 – 1.50 (m, 3H).

Example 221: (R)-(7-(Difluoromethyl)-1H-imidazo[4,5-b]pyridin-2-yl)(5-methyl-7,8-dihydro-1,6-naphthyridin-6(5H)-yl)methanone



[00829] Step A: To a mixture of 4-(difluoromethyl)pyridin-2-amine (2.50 g, 17.3 mmol) in THF (30.0 mL) was added NBS (3.24 g, 18.2 mmol) at 0 °C. The mixture was stirred at 20 °C for 12 h. The mixture was filtered and concentrated under reduced pressure to give a residue which was purified by flash silica gel chromatography using a gradient of EtOAc/petroleum ether from 1/100 to 1/5 to give 5-bromo-4-(difluoromethyl)pyridin-2-amine. LC-MS: 223 [M+H]⁺.

[00830] Step B: To a mixture of 5-bromo-4-(difluoromethyl)pyridin-2-amine (2.00 g, 8.96 mmol) in H₂SO₄ (20.0 mL) was added HNO₃ (1.13 g, 17.9 mmol) dropwise at 0 °C, the mixture was stirred at 20 °C for 2 h. The reaction mixture was poured into H₂O (100 mL) and extracted with DCM (100 mL x 3). The combined organic layers were dried over Na₂SO₄, filtered, and concentrated under vacuum to give a residue which was purified by flash silica gel chromatography using a gradient of EtOAc/petroleum ether from 0/1 to 1/1 to give N-(5-bromo-4-(difluoromethyl)pyridin-2-yl)nitramide. LC-MS: 268.0 [M+H]⁺. ¹H NMR (400 MHz, DMSO-*d*₆) δ 8.78 (s, 1H), 8.01 (s, 1H), 7.39 – 7.02 (m, 1H).

[00831] Step C: A mixture of N-(5-bromo-4-(difluoromethyl)pyridin-2-yl)nitramide (1.40 g, 0.746 mmol) in H₂SO₄ (14.0 mL) was stirred at 50 °C for 2 h. The reaction mixture was poured into H₂O (30.0 mL) and extracted with DCM (50.0 mL x 3). The combined organic layers were dried over Na₂SO₄, filtered, and concentrated under vacuum to give a residue which was purified

by flash silica gel chromatography using a gradient of EtOAc/petroleum ether from 0/1 to 1/1 to give 5-bromo-4-(difluoromethyl)-3-nitropyridin-2-amine. LC-MS: 268.0 [M+H]⁺. ¹H NMR (400 MHz, DMSO-*d*₆) δ 8.49 (s, 1H), 7.36 (br s, 2H), 7.24 – 7.00 (m, 1H).

[00832] Step D: To a solution of Pd/C (297 mg, 10% purity) in THF (6.00 mL) was added 5-bromo-4-(difluoromethyl)-3-nitro-pyridin-2-amine (150 mg, 0.559 mmol) at 20 °C. Then the reaction mixture was stirred at 20 °C for 2 h under H₂ (15 Psi). The reaction mixture was concentrated to give 4-(difluoromethyl)pyridine-2,3-diamine. LC-MS: 160.2 [M+H]⁺. ¹H NMR (400 MHz, DMSO-*d*₆) δ 7.92 (br s, 2H), 7.34 (d, *J* = 6.5 Hz, 1H), 7.18 – 7.01 (m, 1H), 6.85 (d, *J* = 6.5 Hz, 1H), 6.30 (br s, 2H).

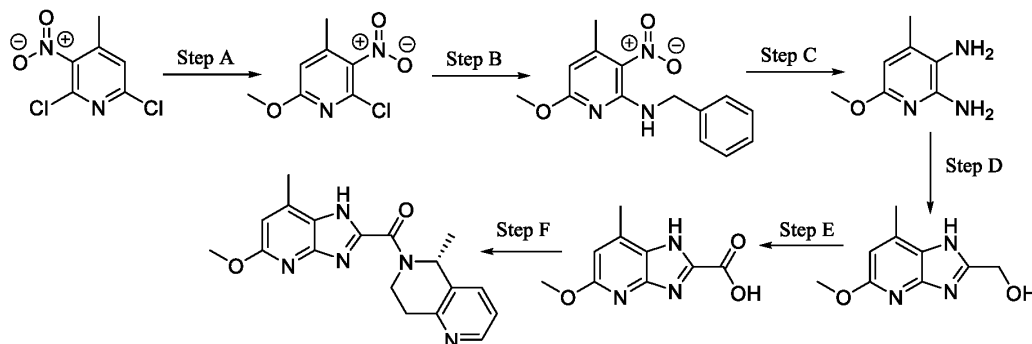
[00833] Step E: A solution of 4-(difluoromethyl)pyridine-2,3-diamine (110 mg, 0.691 mmol) in methyl 2,2,2-trimethoxyacetate (567 mg, 3.46 mmol) was stirred at 100 °C for 12 h. The reaction mixture was concentrated to give a residue which was diluted with H₂O (10.0 mL) and extracted with EtOAc (10.0 mL × 3). The combined organic layers were dried over Na₂SO₄, filtered and the filtrate was concentrated in vacuum to give a residue which was purified by preparative TLC (pure EtOAc) to give methyl 7-(difluoromethyl)-1H-imidazo[4,5-*b*]pyridine-2-carboxylate. ¹H NMR (400 MHz, DMSO-*d*₆) δ 14.74 – 14.32 (m, 1H), 8.68 (br d, *J* = 3.5 Hz, 1H), 7.78 – 7.36 (m, 2H), 3.98 (s, 3H).

[00834] Step F: To a solution of methyl 7-(difluoromethyl)-1H-imidazo[4,5-*b*]pyridine-2-carboxylate (20.0 mg, 0.088 mmol) in dioxane (1.00 mL) was added NaOH (2 M aqueous, 0.769 mL). The mixture was stirred at 80 °C for 6 h. The reaction mixture was allowed to cool to room temperature, poured into water (5.00 mL) and extracted with TBME (5.00 mL × 2). The aqueous phase was adjusted to pH 4 by adding HCl (1 M aqueous) and extracted with EtOAc (5.00 mL × 3). The combined organic layers were dried over Na₂SO₄, filtered, and concentrated under vacuum to give 7-(difluoromethyl)-1H-imidazo[4,5-*b*]pyridine-2-carboxylic acid which was used without further purification. LC-MS: 214.4 [M+H]⁺.

[00835] Step F: To a solution of 7-(difluoromethyl)-1H-imidazo[4,5-*b*]pyridine-2-carboxylic acid (20 mg, 0.093 mmol) and (5R)-5-methyl-5,6,7,8-tetrahydro-1,6-naphthyridine (13.9 mg, 0.093 mmol) in DMF (1.00 mL) was added DIEA (36.4 mg, 0.281 mmol) and HATU (17.8 mg, 0.047 mmol). The mixture was stirred at 20 °C for 1 h. The reaction was purified by preparative HPLC (column: WePure Biotech XP tC18 C18 (150 × 40 mm, 7 μm); flow rate: [H₂O(10mM NH₄HCO₃)-ACN]; gradient: 10% – 40% B over 8 min; mobile phase A: 10mM aqueous NH₄HCO₃, mobile phase B: acetonitrile) to give (R)-(7-(difluoromethyl)-1H-imidazo[4,5-*b*]pyridin-2-yl)(5-methyl-7,8-dihydro-1,6-naphthyridin-6(5H)-yl)methanone. LC-MS: 344.1 [M+H]⁺. ¹H NMR (400 MHz, DMSO-*d*₆) δ 8.58 – 8.49 (m, 1H), 8.45 – 8.34 (m, 1H), 7.82 – 7.59

(m, 1H), 7.55 – 7.33 (m, 2H), 7.32 – 7.14 (m, 1H), 6.07 – 5.67 (m, 1H), 5.08 – 4.64 (m, 1H), 3.75 – 3.53 (m, 1H), 3.24 – 3.13 (m, 1H), 3.03 – 2.89 (m, 1H), 1.67 – 1.54 (m, 3H).

Example 222: (R)-(5-Methoxy-7-methyl-1H-imidazo[4,5-b]pyridin-2-yl)(5-methyl-7,8-dihydro-1,6-naphthyridin-6(5H)-yl)methanone



[00836] Step A: 2,6-Dichloro-4-methyl-3-nitropyridine (5.16 g, 24.2 mmol) was dissolved in MeOH (80.0 mL) at room temperature. The solution was stirred when K_2CO_3 (5.01 g, 36.3 mmol) was added. After stirring overnight, it was diluted with water and extracted with EtOAc. The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4 , filtered and concentrated to give 2-chloro-6-methoxy-4-methyl-3-nitropyridine.

[00837] Step B: 2-Chloro-6-methoxy-4-methyl-3-nitropyridine (161 mg, 0.397 mmol) was dissolved in MeCN (3.00 mL) at room temperature. The solution was stirred when benzylamine (110 μ L, 0.997 mmol) was added. After stirring overnight at room temperature, the flask was equipped with a condenser and heated at 40 °C for 3 h. The mixture was allowed to cool down to room temperature and more benzylamine (110 μ L, 0.997 mmol) was added. Additional benzylamine (110 μ L, 0.997 mmol) was added and stirring was continued for 48 h. The mixture was adsorbed on celite and purified by flash chromatography on silica gel using a solution of EtOAc in heptanes (0 to 100% gradient) to afford N-benzyl-6-methoxy-4-methyl-3-nitropyridin-2-amine. LC-MS: 274.3 $[MH]^+$. 1H NMR (500 MHz, DMSO- d_6) δ 9.11 (t, J = 5.9 Hz, 1H), 7.38 – 7.28 (m, 4H), 7.24 – 7.20 (m, 1H), 6.05 (d, J = 0.8 Hz, 1H), 4.71 (d, J = 6.0 Hz, 2H), 3.76 (s, 3H), 2.45 (d, J = 0.8 Hz, 3H). Structure confirmed by NOESY.

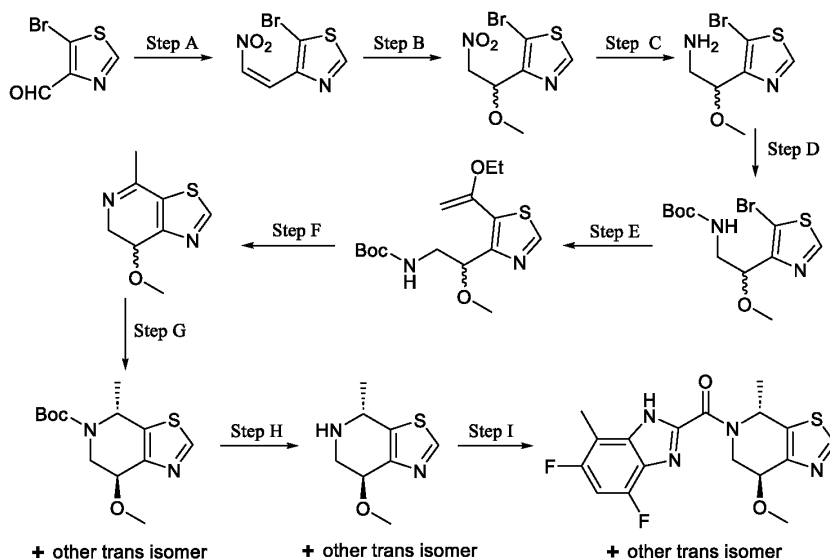
[00838] Step C: 6-Methoxy-4-methylpyridine-2,3-diamine was prepared from N-benzyl-6-methoxy-4-methyl-3-nitropyridin-2-amine according to the procedure of Example 115, Step A. 1H NMR (400 MHz, DMSO- d_6) δ 5.78 (s, 1H), 5.68 – 4.36 (m, 4H), 3.64 (s, 3H), 2.02 (s, 3H).

[00839] Step D: (5-Methoxy-7-methyl-1H-imidazo[4,5-b]pyridin-2-yl)methanol (11 mg, 14%) was prepared from 6-methoxy-4-methylpyridine-2,3-diamine (61.0 mg, 0.398 mmol) according to the procedure of Example 115, Step B. LC-MS: 194.1 $[MH]^+$.

[00840] **Step E:** 5-Methoxy-7-methyl-1H-imidazo[4,5-b]pyridine-2-carboxylic acid was prepared from (5-methoxy-7-methyl-1H-imidazo[4,5-b]pyridin-2-yl)methanol according to the procedure of Example 115, Step D. LC-MS: 208.0 [MH]⁺.

[00841] **Step F:** (R)-(5-Methoxy-7-methyl-1H-imidazo[4,5-b]pyridin-2-yl)(5-methyl-7,8-dihydro-1,6-naphthyridin-6(5H)-yl)methanone (13.0 mg, 35%) was prepared from 5-methoxy-7-methyl-1H-imidazo[4,5-b]pyridine-2-carboxylic acid according to the procedure of Example 115, Step E. LC-MS: 338.2 [MH]⁺. ¹H NMR (400 MHz, DMSO-d₆) δ 8.48 – 8.32 (m, 1H), 7.83 – 7.64 (m, 1H), 7.32 – 7.19 (m, 1H), 6.68 – 6.59 (m, 1H), 6.59 – 4.62 (m, 1H), 3.88 (s, 3H), 3.72 – 3.40 (m, 1H), 3.31 – 2.92 (m, 3H), 2.92 – 2.85 (m, 3H), 1.74 – 1.51 (m, 3H). Rotamers present.

Example 223: rac-trans-(4,6-Difluoro-7-methyl-1H-benzo[d]imidazol-2-yl)(7-methoxy-4-methyl-6,7-dihydrothiazolo [5,4-c]pyridin-5(4H)-yl)methanone



[00842] **Step A:** To a solution of 5-bromothiazole-4-carbaldehyde (1.50 g, 7.82 mmol) in THF (30.0 mL) was added nitromethane (477 mg, 7.81 mmol), pyrrolidine (277 mg, 7.82 mmol) and acetic acid (117 mg, 3.90 mmol). The mixture was stirred at 20 °C for 12 h. The mixture was poured into ice saturation NH₄Cl aqueous (20.0 mL), extracted with EtOAc (20.0 mL x 3). The combined organic layers were concentrated under vacuum to give residue which was purified by flash silica gel chromatography to give (Z)-5-bromo-4-(2-nitrovinyl)thiazole. ¹H NMR (400 MHz, CDCl₃) δ 8.85 (s, 1H), 8.06 – 7.89 (m, 2H).

[00843] **Step B:** To a solution of (Z)-5-bromo-4-(2-nitrovinyl)thiazole (990 mg, 4.21 mmol) in MeOH (36.0 mL) was added a solution of sodium methoxide (56.7 mg, 1.05 mmol) in MeOH (9.00 mL) at 0 °C. The mixture was stirred at 0 °C for 2 h. The mixture was poured into water (60.0 mL) and extracted with EtOAc (30.0 mL x 5). The combined organic layers were dried

over Na₂SO₄, filtered, and concentrated under vacuum to give a residue which was purified by flash silica gel chromatography to give 5-bromo-4-(1-methoxy-2-nitroethyl)thiazole. LC-MS: 267.0 [M+H]⁺.

[00844] Step C: To a solution of 5-bromo-4-(1-methoxy-2-nitroethyl)thiazole (220 mg, 0.822 mmol) in EtOH (8.00 mL) and H₂O (2.00 mL) was added iron powder (230 mg, 4.10 mmol) and ammonium chloride (220 mg, 4.10 mmol). The mixture was stirred at 80 °C for 0.5 h. The mixture was filtered, and the filtrate was concentrated under vacuum to give 2-(5-bromothiazol-4-yl)-2-methoxyethan-1-amine, which was used directly in next step. LC-MS: 237.0 [M+H]⁺.

[00845] Step D: To a solution of 2-(5-bromothiazol-4-yl)-2-methoxyethan-1-amine (190 mg, 0.801 mmol) in EtOH (10.0 mL) was added NaOH (2M aqueous) to adjust pH 10, followed by di-tert-butyl dicarbonate (349 mg, 1.60 mmol). The mixture was stirred at 20 °C for 12 h. The mixture was concentrated under vacuum to give a residue which was purified by preparative TLC to give tert-butyl (2-(5-bromothiazol-4-yl)-2-methoxyethyl)carbamate. ¹H NMR (400 MHz, CDCl₃) δ 8.82 (s, 1H), 5.11 – 4.92 (m, 1H), 4.64 (br t, *J* = 5.9 Hz, 1H), 3.56 (br s, 2H), 3.32 (s, 3H), 1.45 (s, 9H).

[00846] Step E: To a mixture of tert-butyl (2-(5-bromothiazol-4-yl)-2-methoxyethyl)carbamate (160 mg, 0.474 mmol) and tributyl(1-ethoxyvinyl)stannane (342 mg, 948 mmol) in dioxane (8.00 mL) was added Pd(dppf)Cl₂ (17.3 mg, 0.024 mmol). The mixture was stirred at 90 °C for 3 h under a nitrogen atmosphere. The mixture was filtered, and concentrated under vacuum to give a residue which was purified by preparative TLC to give tert-butyl (2-(5-(1-ethoxyvinyl)thiazol-4-yl)-2-methoxyethyl)carbamate. LC-MS: 329.2 [M+H]⁺.

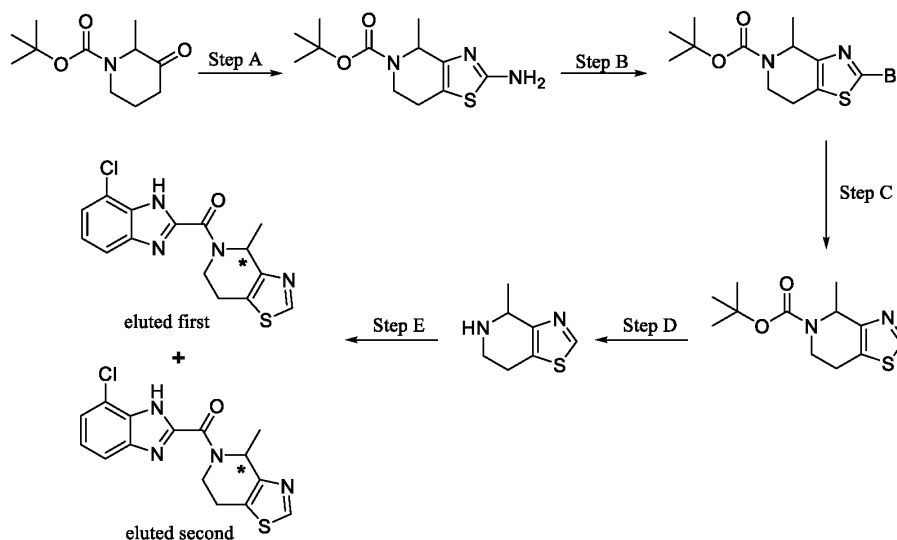
[00847] Step F: To a solution of tert-butyl (2-(5-(1-ethoxyvinyl)thiazol-4-yl)-2-methoxyethyl)carbamate (120 mg, 0.365 mmol) in EtOAc (1.00 mL) was added HCl/EtOAc (4 M, 2.00 mL). The mixture was stirred at 20 °C for 3 h. The mixture was concentrated under vacuum to give 7-methoxy-4-methyl-6,7-dihydrothiazolo[5,4-c]pyridine hydrochloride, which was used directly in next step. LC-MS: 183.1 [M+H]⁺.

[00848] Step G: To a solution of 7-methoxy-4-methyl-6,7-dihydrothiazolo[5,4-c]pyridine hydrochloride (80.0 mg, 0.365 mmol) in MeOH (3.00 mL) was added di-tert-butyl dicarbonate (159 mg, 0.731 mmol) and sodium borohydride (27.7 mg, 0.731 mmol) at 0 °C under a nitrogen atmosphere. The mixture was stirred at 20 °C for 12 h. The mixture was poured into water (5.00 mL) and extracted with EtOAc (10.0 mL x 2). The combined organic layers were dried over Na₂SO₄, filtered, and concentrated under vacuum to give a residue which was purified by preparative TLC to give *trans*-tert-butyl-7-methoxy-4-methyl-6,7-dihydrothiazolo[5,4-c]pyridine-5(4H)-carboxylate. LC-MS: 285.2 [M+H]⁺.

[00849] Step H: To a solution of *trans*-*tert*-butyl 7-methoxy-4-methyl-6,7-dihydrothiazolo[5,4-*c*]pyridine-5(4*H*)-carboxylate (40.0 mg, 0.140 mmol) in EtOAc (2.00 mL) was added HCl/EtOAc (4 M, 4.00 mL). The mixture was stirred at 20 °C for 4 h. The mixture was concentrated under vacuum to give *trans*-7-Methoxy-4-methyl-4,5,6,7-tetrahydrothiazolo[5,4-*c*]pyridine hydrochloride, which was used directly in next step. LC-MS: 185.2 [M+H]⁺.

[00850] Step I: To a solution of *trans*-7-methoxy-4-methyl-4,5,6,7-tetrahydrothiazolo[5,4-*c*]pyridine hydrochloride (30.0 mg, 0.136 mmol) and 4,6-difluoro-7-methyl-1*H*-benzo[*d*]imidazole-2-carboxylic acid (26.0 mg, 0.122 mmol) in THF (2.00 mL) was added BOP-Cl (38.0 mg, 0.075 mmol) and DIEA (44.0 mg, 0.169 mmol). The mixture was stirred at 20 °C for 0.5 h. The mixture was concentrated under vacuum to give a residue which was purified by preparative TLC to give *rac-trans*-(4,6-difluoro-7-methyl-1*H*-benzo[*d*]imidazol-2-yl)(7-methoxy-4-methyl-6,7-dihydrothiazolo[5,4-*c*]pyridin-5(4*H*)-yl)methanone (*trans* racemic). LC-MS: 379.1 [M+H]⁺. ¹H NMR (400 MHz, DMSO-*d*₆) δ 13.92 – 13.62 (m, 1H), 9.18 – 8.93 (m, 1H), 7.30 – 6.36 (m, 1H), 5.91 – 5.59 (m, 1H), 4.95 – 4.49 (m, 1H), 3.78 – 3.55 (m, 3H), 3.42 – 3.35 (m, 1H), 2.48 – 2.38 (m, 4H), 1.77 – 1.53 (m, 3H).

Examples 224A and 224B: (R) or (S)-(7-Chloro-1*H*-benzo[*d*]imidazol-2-yl)(4-methyl-6,7-dihydrothiazolo[4,5-*c*]pyridin-5(4*H*)-yl)methanone and (R) or (S)-(7-Chloro-1*H*-benzo[*d*]imidazol-2-yl)(4-methyl-6,7-dihydrothiazolo[4,5-*c*]pyridin-5(4*H*)-yl)methanone



[00851] Step A: To a solution of *tert*-butyl 2-methyl-3-oxopiperidine-1-carboxylate (1.28 mL, 4.45 mmol) in pyridine (6.00 mL) was added sulfur powder (286 mg, 1.11 mmol) and cyanamide (378 mg, 8.91 mmol). The reaction mixture was stirred for 1h at 130 °C, cooled to room temperature, and then concentrated under reduced pressure. The residue was re-partitioned

between EtOAc and water and washed with brine. The organic solution was dried (Na_2SO_4), filtered, and concentrated under reduced pressure to provide *tert*-butyl 2-amino-4-methyl-6,7-dihydrothiazolo[4,5-*c*]pyridine-5(4*H*)-carboxylate, which was used in the next step without purification. LC-MS: 270.2 $[\text{M}+\text{H}]^+$.

[00852] Step B: To a solution of *tert*-butyl 2-amino-4-methyl-6,7-dihydrothiazolo[4,5-*c*]pyridine-5(4*H*)-carboxylate (1.20 g, 4.45 mmol) in MeCN (45.6 mL) was added copper (II) bromide (2.11 g, 9.36 mmol) followed by isopentyl nitrite (1.30 mL, 9.36 mmol) dropwise. The reaction mixture was stirred at room temperature for 1h. The mixture was concentrated under reduced pressure, re-suspended in EtOAc and filtered through a PTFE frit (0.45 micron). The filtrate was rinsed with aq. sat. NH_4Cl , brine, dried (Na_2SO_4), filtered and concentrated under reduced pressure. The residue was purified by flash column chromatography (0-100% EtOAc/heptanes, 0.5% DCM) to give *tert*-butyl 2-bromo-4-methyl-6,7-dihydrothiazolo[4,5-*c*]pyridine-5(4*H*)-carboxylate. LC-MS: 279.1 $[\text{M}-55]^+$.

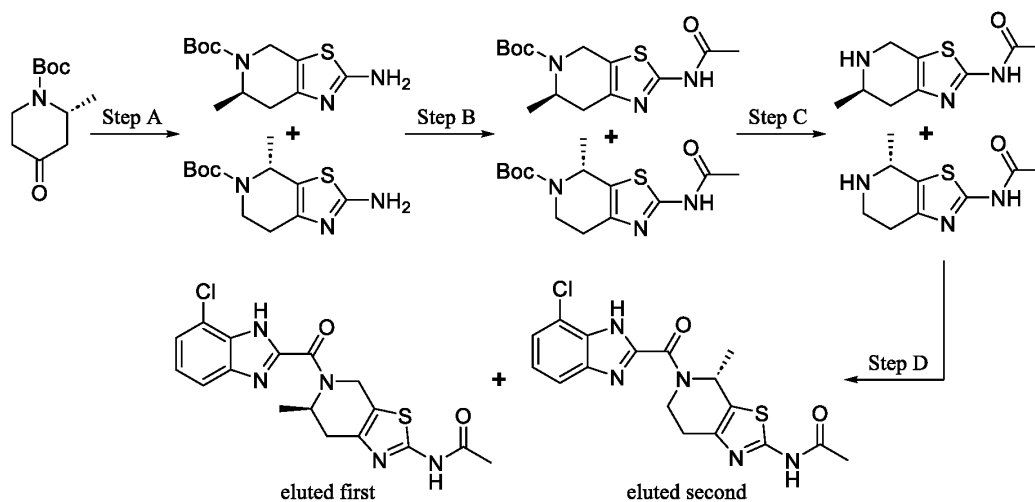
[00853] Step C: A flask containing palladium on carbon 10% loading (63.9 mg, 0.0600 mmol) was evacuated and re-filled with N_2 . A solution of *tert*-butyl 2-bromo-4-methyl-6,7-dihydrothiazolo[4,5-*c*]pyridine-5(4*H*)-carboxylate (400 mg, 1.20 mmol) in $\text{CF}_3\text{CH}_2\text{OH}$ (12.0 mL) was added to the flask. The flask was evacuated and re-filled with H_2 two additional times, and then stirred at room temperature for 3h. The flask was evacuated and replaced with N_2 . The suspension was filtered through a PTFE frit (0.45 micron) and the filtrate was concentrated under reduced pressure to provide *tert*-butyl 4-methyl-6,7-dihydrothiazolo[4,5-*c*]pyridine-5(4*H*)-carboxylate. LC-MS: 255.2 $[\text{M}+\text{H}]^+$.

[00854] Step D: To a solution of *tert*-butyl 4-methyl-6,7-dihydrothiazolo[4,5-*c*]pyridine-5(4*H*)-carboxylate (305 mg, 1.2 mmol) in DCM (12.0 mL) was added trifluoroacetic acid (928 μL , 12.0 mmol). The reaction was stirred for 30 minutes at room temperature and concentrated under reduced pressure and azeotroped with CHCl_3 to provide 4-methyl-4,5,6,7-tetrahydrothiazolo[4,5-*c*]pyridine. LC-MS: 155.1 $[\text{M}+\text{H}]^+$.

[00855] Step E: To a solution of 4-methyl-4,5,6,7-tetrahydrothiazolo[4,5-*c*]pyridine (185 mg, 1.2 mmol) and 7-chloro-1*H*-benzo[*d*]imidazole-2-carboxylic acid (236 mg, 1.20 mmol) in DMF (6.00 mL) with *N,N*-diisopropylethylamine (1.05 mL, 6.00 mmol) was added HATU (456 mg, 1.20 mmol). The reaction mixture was stirred for 16h at room temperature. The mixture was diluted with EtOAc and 10% aqueous lithium chloride solution. The organic layer was washed with 10% aqueous lithium chloride and brine. The organic solution was dried (Na_2SO_4), filtered and concentrated under reduced pressure. The residue was purified by flash column chromatography and then was further separated into its constituent enantiomers by chiral HPLC

(Column: Phenomenex, i-Amylose-3, 5 μ m, 10 x 250 mm. Gradient: 90% A at 8 mL/min for 1 minute, 90% B at 8 mL/min to 90% A at 5 mL/min in 1 minutes, then hold at 90% A at 5 mL/min for 10 minutes. Eluents: A = Acetonitrile; B = Ethanol + 0.1% NH₄OH. Flow: 45 mL/min. Run Time: 12 min) to afford a first eluted compound and a second eluted compound. First eluted compound (**Example 36A**): LC-MS: 333.2 [M+H]⁺. ¹H NMR (400 MHz, DMSO-*d*₆) δ 13.55 (br s, 1H), 9.01 (s, 0.6H), 8.98 (s, 0.4H), 7.58 – 7.44 (m, 0.8H), 7.38 (d, *J* = 7.5 Hz, 1H), 7.34 – 7.28 (m, 1H), 6.65 (br s, 0.2H), 5.73 (br s, 0.4H), 5.67 (q, *J* = 6.7 Hz, 0.6H), 4.82 (dd, *J* = 13.1, 5.0 Hz, 0.4H), 3.62 – 3.51 (m, 1H), 3.33 – 3.25 (m, 0.6H), 3.08 – 2.86 (m, 2H), 1.67 (d, *J* = 6.5 Hz, 1H), 1.55 (d, *J* = 6.7 Hz, 2H). Second eluted compound (**Example 36B**): UPLC-MS: [MH]⁺ = 333.2. ¹H NMR (400 MHz, DMSO-*d*₆) δ 13.55 (br s, 1H), 9.01 (s, 0.6H), 8.98 (s, 0.4H), 7.58 – 7.47 (m, 0.8H), 7.38 (d, *J* = 7.5 Hz, 1H), 7.35 – 7.27 (m, 1H), 6.60 (br s, 0.2H), 5.83 (br s, 0.4H), 5.68 (q, *J* = 6.7 Hz, 0.6H), 4.82 (dd, *J* = 13.0, 4.9 Hz, 0.4H), 3.61 – 3.50 (m, 1H), 3.33 – 3.25 (m, 0.6H), 3.08 – 2.86 (m, 2H), 1.67 (d, *J* = 6.4 Hz, 1H), 1.55 (d, *J* = 6.7 Hz, 2H). The absolute stereochemistry for the first and second eluted compounds was not determined.

Examples 225A and 225B: (*R*)-*N*-(5-(7-Chloro-1*H*-benzo[*d*]imidazole-2-carbonyl)-4-methyl-4,5,6,7-tetrahydrothiazolo[5,4-*c*]pyridin-2-yl)acetamide and (*R*)-*N*-(5-(7-chloro-1*H*-benzo[*d*]imidazole-2-carbonyl)-6-methyl-4,5,6,7-tetrahydrothiazolo[5,4-*c*]pyridin-2-yl)acetamide



[00856] Step A: A solution of (*R*)-*tert*-butyl 2-methyl-4-oxopiperidine-1-carboxylate (2.0 g, 9.10 mmol), sulfur powder (583 mg, 2.27 mmol) and cyanamide (773 mg, 18.2 mmol) in pyridine (12.4 mL) was heated for 2 h at 130 °C. The solution was cooled to room temperature, concentrated under reduced pressure and re-dissolved in EtOAc. The organic solution was washed with 10% aq. LiCl, brine, dried over anhydrous Na₂SO₄. The crude material was

adsorbed onto SiO₂ and purified by flash column chromatography to give 1:1 (*R*)-*tert*-butyl 2-amino-6-methyl-6,7-dihydrothiazolo[5,4-*c*]pyridine-5(4*H*)-carboxylate and (*R*)-*tert*-butyl 2-amino-4-methyl-6,7-dihydrothiazolo[5,4-*c*]pyridine-5(4*H*)-carboxylate. LC-MS: 270.3 [M+H]⁺.

[00857] Step B: To a solution of a mixture of (*R*)-*tert*-butyl 2-amino-6-methyl-6,7-dihydrothiazolo[5,4-*c*]pyridine-5(4*H*)-carboxylate and (*R*)-*tert*-butyl 2-amino-4-methyl-6,7-dihydrothiazolo[5,4-*c*]pyridine-5(4*H*)-carboxylate (60.0 mg, 0.223 mmol) in pyridine (2.20 mL) was added acetic anhydride (213 μ L, 2.23 mmol) and stirred for 16 h at 25 °C. The solution was concentrated under reduced pressure and re-partitioned between 2-methyltetrahydrofuran and water, then basified to pH 7 with aq. sat. NaHCO₃. The organic layer was washed with brine (1x) and dried (Na₂SO₄). The solution was filtered and concentrated under reduced pressure to give a mixture of (*R*)-*tert*-butyl 2-acetamido-4-methyl-6,7-dihydrothiazolo[5,4-*c*]pyridine-5(4*H*)-carboxylate and (*R*)-*tert*-butyl 2-acetamido-6-methyl-6,7-dihydrothiazolo[5,4-*c*]pyridine-5(4*H*)-carboxylate, which was used without purification in the next step. LC-MS: 312.3 [M+H]⁺.

[00858] Step C: Prepared as in Examples 36A and 36B, Step D using 1:1 (*R*)-*tert*-butyl 2-acetamido-6-methyl-6,7-dihydrothiazolo[5,4-*c*]pyridine-5(4*H*)-carboxylate and (*R*)-*tert*-butyl 2-acetamido-4-methyl-6,7-dihydrothiazolo[5,4-*c*]pyridine-5(4*H*)-carboxylate (138.8 mg, 0.446 mmol) to afford a 1:1 mixture of (*R*)-*N*-(6-methyl-4,5,6,7-tetrahydrothiazolo[5,4-*c*]pyridin-2-yl)acetamide and (*R*)-*N*-(4-methyl-4,5,6,7-tetrahydrothiazolo[5,4-*c*]pyridin-2-yl)acetamide, which was used without further purification. LC-MS: 212.2 [M+H]⁺.

[00859] Step D: Prepared according to Examples 42A, 42B, 42C, and 42D step D using 7-chloro-2-(trichloromethyl)-1*H*-benzo[*d*]imidazole (126 mg, 0.468 mmol) and a 1:1 mixture of (*R*)-*N*-(4-methyl-4,5,6,7-tetrahydrothiazolo[5,4-*c*]pyridin-2-yl)acetamide and (*R*)-*N*-(6-methyl-4,5,6,7-tetrahydrothiazolo[5,4-*c*]pyridin-2-yl)acetamide (94.2 mg, 0.446 mmol). (*R*)-*N*-(5-(7-chloro-1*H*-benzo[*d*]imidazole-2-carbonyl)-6-methyl-4,5,6,7-tetrahydrothiazolo[5,4-*c*]pyridin-2-yl)acetamide first eluent) and (*R*)-*N*-(5-(7-chloro-1*H*-benzo[*d*]imidazole-2-carbonyl)-4-methyl-4,5,6,7-tetrahydrothiazolo[5,4-*c*]pyridin-2-yl)acetamide (second eluent). First eluted: LC-MS: 388.6 [M+H]⁺. ¹H NMR (400 MHz, DMSO-*d*₆) δ 8.34 (s, 2H), 7.56 (t, *J* = 7.6 Hz, 1H), 7.37 (d, *J* = 7.6 Hz, 1H), 7.31 (t, *J* = 7.8 Hz, 1H), 6.12 (d, *J* = 16.8 Hz, 0.4H), 5.84 – 5.74 (m, 0.6H), 5.38 (d, *J* = 17.3 Hz, 0.6H), 5.32 – 5.24 (m, 0.4H), 4.61 (d, *J* = 17.1 Hz, 0.4H), 4.26 (d, *J* = 17.4 Hz, 0.6H), 3.11 – 3.03 (m, 0.6H), 2.98 – 2.90 (m, 0.4H), 2.64 – 2.56 (m, 1H), 2.11 (d, *J* = 6.8 Hz, 3H), 1.25 (d, *J* = 6.6 Hz, 3H). Second eluted: LC-MS: 390.5 [M+H]⁺. ¹H NMR (400 MHz, DMSO-*d*₆) δ 12.14 (br s, 1H), 7.55 (d, *J* = 7.8 Hz, 1H), 7.38 (d, *J* = 7.6 Hz, 1H), 7.31 (t, *J* = 7.8 Hz, 1H), 6.46 – 6.34 (m, 0.3H), 5.75 (q, *J* = 6.3 Hz, 0.7H), 5.66 – 5.47 (m, 0.65H), 4.79 – 4.70 (m, *J* = 12.9 Hz, 0.35H), 3.62 – 3.54 (m, 1H), 2.95 – 2.84 (m, 1H), 2.77 – 2.71 (m, 1H), 2.13 (s,

2H), 2.11 (s, 1H), 1.67 (d, $J = 6.5$ Hz, 1H), 1.52 (d, $J = 6.6$ Hz, 2H). Regioisomers were tentatively assigned.

Example 226: Assay Protocol

[00860] The following assay protocol was followed:

Day 1 - Seed cells

1. Added 6 mL TrypLE select to T175 flask and incubated for 2-3 minutes
2. Added 12 mL DMEM+10% qFBS and collect cells in a 50 mL conical tube
3. Counted cells and transferred the desired amount to a new 50 mL conical tube
4. Centrifuged cells at 150 x g for 3 minutes
5. Resuspended cells to 6e5 cells/mL in DMEM+10% qFBS
6. Dispensed 25 uL/well (15k cells/well) into PLL:Collagen coated 384 well black plates
7. Pulsed spin plates
8. Incubated plates overnight at 37° C

Day 2 - Dox and dose cells

1. Prepared drug plates at 6x final screening concentration. Ensured the final DMSO concentration in the assay plate does not exceed 1%.
2. Prepared 6x Doxycycline media at 12uM final concentration in Opti-MEM.
3. Dispensed 15ul of Doxycycline Opti-MEM mixture into the drug plate.
4. Mixed wells thoroughly and stamp 5ul of Opti-MEM drug mixture from drug plates into assay plates.
5. Pulsed spin plates
6. Incubated plates overnight at 37° C

Day 3 - Add detection and read

0. Prepared Nano-Glo HiBiT Extracellular Detection System (Promega) reagent
 - a. Made fresh every time: 10mL Extracellular Buffer with 100uL of LgBiT protein and 200uL Extracellular Substrate.
1. Mixed reagent 1:1 with OptiMEM
2. Flicked media and blotted on a dry kimwipe to remove residual liquid. Dispensed 30uL of 1:1 Opti-MEM, HiBiT surface expression reagent into each well.
3. Shook plates at 300-500rpm for 3-10 minutes.
4. Read Luminescence at an integration time of 500 ms

[00861] EC_{50} data according to the assay described above is provided in Table 1.

$+= -4 (\log_{10}([M])) > EC_{50} \geq -5 (\log_{10}([M]))$; $++ = -5 (\log_{10}([M])) > EC_{50} \geq -5.7 (\log_{10}([M]))$;
 $+++ = EC_{50} < -5.7 (\log_{10}([M]))$; ND = not active in top assay concentration tested (20 uM).

Table 1

Example No.	EC ₅₀	Example No.	EC ₅₀	Example No.	EC ₅₀
1	+	82	++	162	ND
2	+	83	ND	163	+
3	+	84	++	164	+++
4	+	85	+	165	ND
4A	++	86	++	166	ND
4B	+	87	+	167A	+
5	+	88	++	167B	+++
6	ND	88A	+++	168A	ND
7	+	88B	+	168B	ND
8	+	88C	ND	169A	+
9	+++	88D	ND	169B	ND
10	+++	89	+++	170A	+
10A	++	90A	+	170B	+++
10B	+++	90B	+	171A	+++
11	++	91	+++	171B	+
12	ND	92	+	172A	ND
13	++	93	ND	172B	++
14	++	94	+	173A	+
15	+++	95	ND	173B	ND
15A	+++	96	++	174A	+++
15B	++	97	+	174B	+
16	+	98	ND	175A	++
17	+	99	ND	175B	ND
18	++	100	+	176	++
19	+	101	ND	177	+++
20	+	102	++	178	+++
21	++	103	ND	179	+++
22	+	104	+	180	+++
23	ND	105	ND	181	+++
24A	+++	106	+++	182	+
24B	+	107	ND	183A	+++
25	ND	108	ND	183B	++
26	++	109	+++	184	+++
26A	ND	110	+++	185	ND
26B	+++	111	ND	186	+++
27	+	112	+	187	ND
27A	ND	113A	++	188A	ND
27B	++	113B	++	188B	+++
28A	++	113C	++	189	+++
28B	++	113D	+	190	+
29A	++	114	ND	191A	+
29B	++	115	++	191B	+++
30	+++	116	+++	192A	ND
31	+++	117	+	192B	+++

Example No.	EC ₅₀	Example No.	EC ₅₀	Example No.	EC ₅₀
32	+++	118	ND	193	+++
33	+	119	+++	193A	+++
34	+	120	++	193B	ND
35	++	121A	++	194	+++
36A	++	121B	++	194A	ND
36B	ND	122	++	194B	+++
37	++	123	+++	195A	+++
38	++	123A	ND	195B	++
39	ND	123B	+++	196A	+++
40	++	124	+	196B	++
41	+++	125	++	197A	ND
42	+++	126	+++	197B	+++
43	+	127	ND	198	+++
44	++	128	ND	199	+++
45	+++	129	+++	200A	+++
46	+	130A	++	200B	+
47	++	130B	++	201A	ND
48	+++	131	+++	201B	+++
48A	+++	132	++	202	+++
49A	++	133	+++	203A	+
49B	++	134	+++	203B	+++
50	ND	135	+++	204	+++
51	+	136	+++	205A	ND
52A	+++	137	+++	205B	+
52B	ND	138	+	206A	ND
53	ND	139	+++	206B	+++
54	+++	140A	ND	207A	+++
54A	+	140B	+	207B	ND
54B	+++	140C	++	208A	ND
55	+	140D	ND	208B	+
56	++	140E	ND	209A	ND
57	+++	140F	+	209B	+
58	+++	141A	ND	210A	+++
58A	+++	141B	+	210B	ND
58B	+	142	ND	211A	+++
59	++	142A	ND	211B	ND
60	+	142B	ND	212A	+
61	+	143	ND	212B	+++
62	+	144	+	213A	+
63	+	145	+	213B	+++
64	++	146	+++	214	+++
65	++	146A	ND	215	+
66	+	146B	+++	216A	+++
67	++	147	++	217A	+
68	+++	147A	++	217B	+++
69	++	147B	ND	218	+++

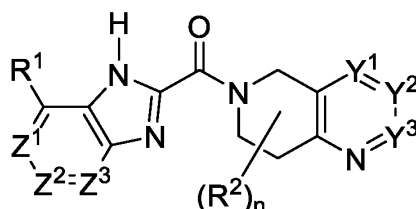
Example No.	EC ₅₀	Example No.	EC ₅₀	Example No.	EC ₅₀
70	+++	148A	ND	219	+++
70A	+++	148B	+++	220	+++
70B	ND	149	++	221	+
71	+	150	+	222	+++
72	++	151	ND	223	++
73	++	152	ND	224A	+
74A	+	153	+	224B	++
74B	++	154	ND	225A	ND
74C	++	155	ND	225B	ND
74D	ND	156	ND		
75	+++	157	ND		
76	ND	157A	ND		
77	ND	157B	++		
78	++	158	ND		
79	+++	159	+		
80	+	160	+++		
81	+++	161	ND		

[00862] The examples and embodiments described herein are for illustrative purposes only and various modifications or changes suggested to persons skilled in the art are to be included within the spirit and purview of this application and scope of the appended claims.

CLAIMS

WHAT IS CLAIMED IS:

1. A compound of Formula (I), or a pharmaceutically acceptable salt or solvate thereof:



Formula (I);

wherein:

Y¹, Y², and Y³ are each independently C(R³) or N, wherein at least one of Y² and Y³ is C(R³);

Z¹, Z², and Z³ are each independently C(R⁴) or N, wherein at least one of Z¹, Z², and Z³ is C(R⁴);

R¹ is selected from hydrogen, halogen, -CN, -OR¹⁰, -SR¹⁰, -N(R¹⁰)(R¹¹), -C(O)OR¹⁰, -OC(O)N(R¹⁰)(R¹¹), -N(R¹²)C(O)N(R¹⁰)(R¹¹), -N(R¹²)C(O)OR¹³, -N(R¹²)S(O)₂R¹³, -C(O)R¹³, -S(O)R¹³, -OC(O)R¹³, -C(O)N(R¹⁰)(R¹¹), -N(R¹²)C(O)R¹³, -S(O)₂R¹³, -S(O)₂N(R¹⁰)(R¹¹)-, -S(=O)(=NH)N(R¹⁰)(R¹¹), C₁₋₆alkyl, C₁₋₆haloalkyl, C₂₋₆alkenyl, C₂₋₆alkynyl, C₃₋₆cycloalkyl, C₂₋₉heterocycloalkyl, C₆₋₁₀aryl, and C₁₋₉heteroaryl, wherein C₁₋₆alkyl, C₁₋₆haloalkyl, C₂₋₆alkenyl, C₂₋₆alkynyl, C₃₋₆cycloalkyl, C₂₋₉heterocycloalkyl, C₆₋₁₀aryl, and C₁₋₉heteroaryl are optionally substituted with 1-5 R^{5a} groups;

each R² is independently selected from halogen, -CN, -OR¹⁰, -SR¹⁰, -N(R¹⁰)(R¹¹), C₁₋₆alkyl, C₁₋₆haloalkyl, C₂₋₆alkenyl, C₂₋₆alkynyl, C₃₋₆cycloalkyl, C₂₋₉heterocycloalkyl, C₆₋₁₀aryl, and C₁₋₉heteroaryl, wherein C₁₋₆alkyl, C₁₋₆haloalkyl, C₂₋₆alkenyl, C₂₋₆alkynyl, C₃₋₆cycloalkyl, C₂₋₉heterocycloalkyl, C₆₋₁₀aryl, and C₁₋₉heteroaryl are optionally substituted with 1-5 R^{5b} groups;

each R³ is independently selected from hydrogen, halogen, -CN, -SR¹⁰, -N(R¹⁰)(R¹¹), C₁₋₆alkyl, C₁₋₆haloalkyl, C₁₋₆alkoxy, C₂₋₆alkenyl, C₂₋₆alkynyl, C₃₋₆cycloalkyl, C₂₋₉heterocycloalkyl, C₆₋₁₀aryl, and C₁₋₉heteroaryl, wherein C₁₋₆alkyl, C₁₋₆haloalkyl, C₁₋₆alkoxy, C₂₋₆alkenyl, C₂₋₆alkynyl, C₃₋₆cycloalkyl, C₂₋₉heterocycloalkyl, C₆₋₁₀aryl, and C₁₋₉heteroaryl are optionally substituted with 1-5 R^{5c} groups;

each R⁴ is independently selected from hydrogen, halogen, -CN, -OR¹⁰, -SR¹⁰, -N(R¹⁰)(R¹¹), C₁₋₆alkyl, C₁₋₆haloalkyl, C₂₋₆alkenyl, C₂₋₆alkynyl, C₃₋₆cycloalkyl, C₂₋₉heterocycloalkyl,

C₆₋₁₀aryl, and C₁₋₉heteroaryl, wherein C₁₋₆alkyl, C₁₋₆haloalkyl, C₂₋₆alkenyl, C₂₋₆alkynyl, C₃₋₆cycloalkyl, C₂₋₉heterocycloalkyl, C₆₋₁₀aryl, and C₁₋₉heteroaryl are optionally substituted with 1-5 R^{5d} groups;

each R^{5a}, R^{5b}, R^{5c}, and R^{5d} is each independently selected from halogen, oxo, -CN, C₁₋₆alkyl, C₁₋₆haloalkyl, C₂₋₆alkenyl, C₂₋₆alkynyl, C₃₋₆cycloalkyl, -CH₂-C₃₋₆cycloalkyl, C₂₋₉heterocycloalkyl, -CH₂-C₂₋₉heterocycloalkyl, C₆₋₁₀aryl, -CH₂-C₆₋₁₀aryl, C₁₋₉heteroaryl, -CH₂-C₁₋₉heteroaryl, -OR¹⁰, -SR¹⁰, -N(R¹⁰)(R¹¹), -C(O)OR¹⁰, -OC(O)N(R¹⁰)(R¹¹), -N(R¹²)C(O)N(R¹⁰)(R¹¹), -N(R¹²)C(O)OR¹³, -N(R¹²)S(O)₂R¹³, -C(O)R¹³, -S(O)R¹³, -OC(O)R¹³, -C(O)N(R¹⁰)(R¹¹), -C(O)C(O)N(R¹⁰)(R¹¹), -N(R¹²)C(O)R¹³, -S(O)₂R¹³, -S(O)₂N(R¹⁰)(R¹¹), -S(=O)(=NH)N(R¹⁰)(R¹¹), -C(=NOR¹¹)R¹³, -CH₂C(O)N(R¹⁰)(R¹¹), -CH₂N(R¹²)C(O)R¹³, -CH₂S(O)₂R¹³, and -CH₂S(O)₂N(R¹⁰)(R¹¹), wherein C₁₋₆alkyl, C₁₋₆haloalkyl, C₂₋₆alkenyl, C₂₋₆alkynyl, C₃₋₆cycloalkyl, -CH₂-C₃₋₆cycloalkyl, C₂₋₉heterocycloalkyl, -CH₂-C₂₋₉heterocycloalkyl, C₆₋₁₀aryl, -CH₂-C₆₋₁₀aryl, C₁₋₉heteroaryl, -CH₂-C₁₋₉heteroaryl are optionally substituted with one, two, or three groups selected from halogen, -CN, C₁₋₆alkyl, C₁₋₆haloalkyl, C₃₋₆cycloalkyl, C₂₋₉heterocycloalkyl, C₆₋₁₀aryl, C₁₋₉heteroaryl, -OR¹⁰, and -N(R¹⁰)(R¹¹);

each R¹⁰ is independently selected from hydrogen, C₁₋₆alkyl, C₁₋₆ haloalkyl, C₂₋₆alkenyl, C₂₋₆alkynyl, C₃₋₆cycloalkyl, C₂₋₉heterocycloalkyl, C₆₋₁₀aryl, and C₁₋₉heteroaryl, wherein C₁₋₆alkyl, C₂₋₆alkenyl, C₂₋₆alkynyl, C₃₋₆cycloalkyl, C₂₋₉heterocycloalkyl, C₆₋₁₀aryl, and C₁₋₉heteroaryl are optionally substituted with one, two, or three groups selected from halogen, -CN, hydroxy, C₁₋₆alkyl, C₁₋₆haloalkyl, C₁₋₆alkoxy, C₃₋₆cycloalkyl, C₂₋₉heterocycloalkyl, C₆₋₁₀aryl, and C₁₋₉heteroaryl;

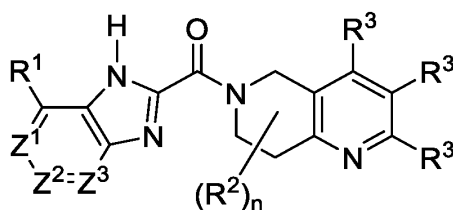
each R¹¹ is independently selected from hydrogen, C₁₋₆alkyl, and C₁₋₆haloalkyl;

each R¹² is independently selected from hydrogen, C₁₋₆alkyl, and C₁₋₆haloalkyl;

each R¹³ is independently selected C₁₋₆alkyl, C₂₋₆alkenyl, C₂₋₆alkynyl, C₃₋₆cycloalkyl, C₂₋₉heterocycloalkyl, C₆₋₁₀aryl, and C₁₋₉heteroaryl, wherein C₁₋₆alkyl, C₂₋₆alkenyl, C₂₋₆alkynyl, C₃₋₆cycloalkyl, C₂₋₉heterocycloalkyl, C₆₋₁₀aryl, and C₁₋₉heteroaryl are optionally substituted with one, two, or three groups selected from halogen, -CN, hydroxy, C₁₋₆alkyl, C₁₋₆haloalkyl, C₁₋₆alkoxy, C₃₋₆cycloalkyl, C₂₋₉heterocycloalkyl, C₆₋₁₀aryl, and C₁₋₉heteroaryl; and

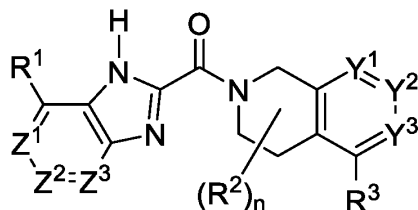
n is 0, 1, 2, 3, or 4.

2. The compound of claim 1, or a pharmaceutically acceptable salt or solvate thereof, having the structure of Formula (Ia):



Formula (Ia).

3. A compound of Formula (II), or a pharmaceutically acceptable salt or solvate thereof:



Formula (II);

wherein:

Y¹, Y², and Y³ are each independently C(R³) or N, wherein at least one of Y¹, Y², and Y³ is C(R³);

Z¹, Z², and Z³ are each independently C(R⁴) or N, wherein at least one of Z¹, Z², and Z³ is C(R⁴);

R¹ is selected from halogen, -CN, -OR¹⁰, -SR¹⁰, -N(R¹⁰)(R¹¹), C₁-₆alkyl, C₁-₆haloalkyl, C₂-₆alkenyl, C₂-₆alkynyl, C₃-₆cycloalkyl, C₂-₉heterocycloalkyl, C₆-₁₀aryl, and C₁-₉heteroaryl, wherein C₁-₆alkyl, C₁-₆haloalkyl, C₂-₆alkenyl, C₂-₆alkynyl, C₃-₆cycloalkyl, C₂-₉heterocycloalkyl, C₆-₁₀aryl, and C₁-₉heteroaryl are optionally substituted with 1-5 R⁵ᵃ groups;

each R² is independently selected from halogen, -CN, -OR¹⁰, -SR¹⁰, -N(R¹⁰)(R¹¹), C₁-₆alkyl, C₁-₆haloalkyl, C₂-₆alkenyl, C₂-₆alkynyl, C₃-₆cycloalkyl, C₂-₉heterocycloalkyl, C₆-₁₀aryl, and C₁-₉heteroaryl, wherein C₁-₆alkyl, C₁-₆haloalkyl, C₂-₆alkenyl, C₂-₆alkynyl, C₃-₆cycloalkyl, C₂-₉heterocycloalkyl, C₆-₁₀aryl, and C₁-₉heteroaryl are optionally substituted with 1-5 R⁵ᵇ groups; or two R² groups on different carbon atoms are taken together to form a bridge that is -CH₂CH₂-;

each R³ is independently selected from hydrogen, halogen, -CN, -SR¹⁰, -N(R¹⁰)(R¹¹), C₁-₆alkyl, C₁-₆haloalkyl, C₁-₆alkoxy, C₂-₆alkenyl, C₂-₆alkynyl, C₃-₆cycloalkyl, C₂-₉heterocycloalkyl, C₆-₁₀aryl, and C₁-₉heteroaryl, wherein C₁-₆alkyl, C₁-₆haloalkyl, C₁-₆alkoxy, C₂-₆alkenyl, C₂-₆alkynyl, C₃-₆cycloalkyl, C₂-₉heterocycloalkyl, C₆-₁₀aryl, and C₁-₉heteroaryl are optionally substituted with 1-5 R⁵ᶜ groups;

each R⁴ is independently selected from hydrogen, halogen, -CN, -OR¹⁰, -SR¹⁰, -N(R¹⁰)(R¹¹), C₁₋₆alkyl, C₁₋₆haloalkyl, C₂₋₆alkenyl, C₂₋₆alkynyl, C₃₋₆cycloalkyl, C₂₋₉heterocycloalkyl, C₆₋₁₀aryl, and C₁₋₉heteroaryl, wherein C₁₋₆alkyl, C₁₋₆haloalkyl, C₂₋₆alkenyl, C₂₋₆alkynyl, C₃₋₆cycloalkyl, C₂₋₉heterocycloalkyl, C₆₋₁₀aryl, and C₁₋₉heteroaryl are optionally substituted with 1-5 R^{5d} groups;

each R^{5a}, R^{5b}, R^{5c}, and R^{5d} is each independently selected from halogen, oxo, -CN, C₁₋₆alkyl, C₁₋₆haloalkyl, C₂₋₆alkenyl, C₂₋₆alkynyl, C₃₋₆cycloalkyl, -CH₂-C₃₋₆cycloalkyl, C₂₋₉heterocycloalkyl, -CH₂-C₂₋₉heterocycloalkyl, C₆₋₁₀aryl, -CH₂-C₆₋₁₀aryl, C₁₋₉heteroaryl, -CH₂-C₁₋₉heteroaryl, -OR¹⁰, -SR¹⁰, -N(R¹⁰)(R¹¹), -C(O)OR¹⁰, -OC(O)N(R¹⁰)(R¹¹), -N(R¹²)C(O)N(R¹⁰)(R¹¹), -N(R¹²)C(O)OR¹³, -N(R¹²)S(O)₂R¹³, -C(O)R¹³, -S(O)R¹³, -OC(O)R¹³, -C(O)N(R¹⁰)(R¹¹), -C(O)C(O)N(R¹⁰)(R¹¹), -N(R¹²)C(O)R¹³, -S(O)₂R¹³, -S(O)₂N(R¹⁰)(R¹¹), -S(=O)(=NH)N(R¹⁰)(R¹¹), -C(=NOR¹¹)R¹³, -CH₂C(O)N(R¹⁰)(R¹¹), -CH₂N(R¹²)C(O)R¹³, -CH₂S(O)₂R¹³, and -CH₂S(O)₂N(R¹⁰)(R¹¹), wherein C₁₋₆alkyl, C₁₋₆haloalkyl, C₂₋₆alkenyl, C₂₋₆alkynyl, C₃₋₆cycloalkyl, -CH₂-C₃₋₆cycloalkyl, C₂₋₉heterocycloalkyl, -CH₂-C₂₋₉heterocycloalkyl, C₆₋₁₀aryl, -CH₂-C₆₋₁₀aryl, C₁₋₉heteroaryl, -CH₂-C₁₋₉heteroaryl are optionally substituted with one, two, or three groups selected from halogen, -CN, C₁₋₆alkyl, C₁₋₆haloalkyl, C₃₋₆cycloalkyl, C₂₋₉heterocycloalkyl, C₆₋₁₀aryl, C₁₋₉heteroaryl, -OR¹⁰, and -N(R¹⁰)(R¹¹);

each R¹⁰ is independently selected from hydrogen, C₁₋₆alkyl, C₁₋₆haloalkyl, C₂₋₆alkenyl, C₂₋₆alkynyl, C₃₋₆cycloalkyl, C₂₋₉heterocycloalkyl, C₆₋₁₀aryl, and C₁₋₉heteroaryl, wherein C₁₋₆alkyl, C₂₋₆alkenyl, C₂₋₆alkynyl, C₃₋₆cycloalkyl, C₂₋₉heterocycloalkyl, C₆₋₁₀aryl, and C₁₋₉heteroaryl are optionally substituted with one, two, or three groups selected from halogen, -CN, hydroxy, C₁₋₆alkyl, C₁₋₆haloalkyl, C₁₋₆alkoxy, C₃₋₆cycloalkyl, C₂₋₉heterocycloalkyl, C₆₋₁₀aryl, and C₁₋₉heteroaryl;

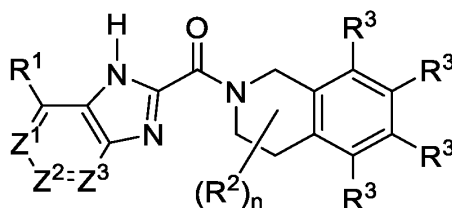
each R¹¹ is independently selected from hydrogen, C₁₋₆alkyl, and C₁₋₆haloalkyl;

each R¹² is independently selected from hydrogen, C₁₋₆alkyl, and C₁₋₆haloalkyl;

each R¹³ is independently selected C₁₋₆alkyl, C₂₋₆alkenyl, C₂₋₆alkynyl, C₃₋₆cycloalkyl, C₂₋₉heterocycloalkyl, C₆₋₁₀aryl, and C₁₋₉heteroaryl, wherein C₁₋₆alkyl, C₂₋₆alkenyl, C₂₋₆alkynyl, C₃₋₆cycloalkyl, C₂₋₉heterocycloalkyl, C₆₋₁₀aryl, and C₁₋₉heteroaryl are optionally substituted with one, two, or three groups selected from halogen, -CN, hydroxy, C₁₋₆alkyl, C₁₋₆haloalkyl, C₁₋₆alkoxy, C₃₋₆cycloalkyl, C₂₋₉heterocycloalkyl, C₆₋₁₀aryl, and C₁₋₉heteroaryl; and

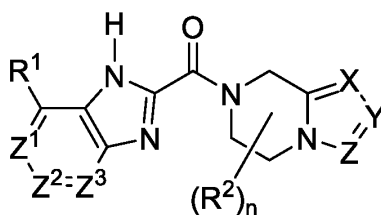
n is 1, 2, 3, or 4.

4. The compound of claim 3, or a pharmaceutically acceptable salt or solvate thereof, having the structure of Formula (IIa):



Formula (IIa).

5. A compound of Formula (III), or a pharmaceutically acceptable salt or solvate thereof:



Formula (III);

wherein:

X, Y and Z are each independently C(R³) or N, wherein at least one of Y and Z is C(R³); Z¹, Z², and Z³ are each independently C(R⁴) or N, wherein at least one of Z¹, Z², and Z³ is C(R⁴);

R¹ is selected from halogen, -CN, -OR¹⁰, -SR¹⁰, -N(R¹⁰)(R¹¹), C₁₋₆alkyl, C₁₋₆haloalkyl, C₂₋₆alkenyl, C₂₋₆alkynyl, C₃₋₆cycloalkyl, C₆₋₁₀aryl, and C₁₋₉heteroaryl, wherein C₁₋₆alkyl, C₁₋₆haloalkyl, C₂₋₆alkenyl, C₂₋₆alkynyl, C₃₋₆cycloalkyl, C₆₋₁₀aryl, and C₁₋₉heteroaryl are optionally substituted with 1-5 R^{5a} groups;

each R² is independently selected from halogen, -CN, -OR¹⁰, -SR¹⁰, -N(R¹⁰)(R¹¹), C₁₋₆alkyl, C₁₋₆haloalkyl, C₂₋₆alkenyl, C₂₋₆alkynyl, C₃₋₆cycloalkyl, C₂₋₉heterocycloalkyl, C₆₋₁₀aryl, and C₁₋₉heteroaryl, wherein C₁₋₆alkyl, C₁₋₆haloalkyl, C₂₋₆alkenyl, C₂₋₆alkynyl, C₃₋₆cycloalkyl, C₂₋₉heterocycloalkyl, C₆₋₁₀aryl, and C₁₋₉heteroaryl are optionally substituted with 1-5 R^{5b} groups;

each R³ is independently selected from hydrogen, halogen, -CN, -SR¹⁰, -N(R¹⁰)(R¹¹), C₁₋₆alkyl, C₁₋₆haloalkyl, C₁₋₆alkoxy, C₂₋₆alkenyl, C₂₋₆alkynyl, C₃₋₆cycloalkyl, C₂₋₉heterocycloalkyl, C₆₋₁₀aryl, and C₁₋₉heteroaryl, wherein C₁₋₆alkyl, C₁₋₆haloalkyl, C₁₋₆alkoxy, C₂₋₆alkenyl, C₂₋₆alkynyl, C₃₋₆cycloalkyl, C₂₋₉heterocycloalkyl, C₆₋₁₀aryl, and C₁₋₉heteroaryl are optionally substituted with 1-5 R^{5c} groups;

each R⁴ is independently selected from hydrogen, halogen, -CN, -OR¹⁰, -SR¹⁰, -N(R¹⁰)(R¹¹), C₁₋₆alkyl, C₁₋₆haloalkyl, C₂₋₆alkenyl, C₂₋₆alkynyl, C₃₋₆cycloalkyl, C₂₋₉heterocycloalkyl, C₆₋₁₀aryl, and C₁₋₉heteroaryl, wherein C₁₋₆alkyl, C₁₋₆haloalkyl, C₂₋₆alkenyl, C₂₋₆alkynyl, C₃₋₆cycloalkyl, C₂₋₉heterocycloalkyl, C₆₋₁₀aryl, and C₁₋₉heteroaryl are optionally substituted with 1-5 R^{5d} groups;

each R^{5a}, R^{5b}, R^{5c}, and R^{5d} is each independently selected from halogen, oxo, -CN, C₁₋₆alkyl, C₁₋₆haloalkyl, C₂₋₆alkenyl, C₂₋₆alkynyl, C₃₋₆cycloalkyl, -CH₂-C₃₋₆cycloalkyl, C₂₋₉heterocycloalkyl, -CH₂-C₂₋₉heterocycloalkyl, C₆₋₁₀aryl, -CH₂-C₆₋₁₀aryl, C₁₋₉heteroaryl, -CH₂-C₁₋₉heteroaryl, -OR¹⁰, -SR¹⁰, -N(R¹⁰)(R¹¹), -C(O)OR¹⁰, -OC(O)N(R¹⁰)(R¹¹), -N(R¹²)C(O)N(R¹⁰)(R¹¹), -N(R¹²)C(O)OR¹³, -N(R¹²)S(O)₂R¹³, -C(O)R¹³, -S(O)R¹³, -OC(O)R¹³, -C(O)N(R¹⁰)(R¹¹), -C(O)C(O)N(R¹⁰)(R¹¹), -N(R¹²)C(O)R¹³, -S(O)₂R¹³, -S(O)₂N(R¹⁰)(R¹¹), -S(=O)(=NH)N(R¹⁰)(R¹¹), -C(=NOR¹¹)R¹³, -CH₂C(O)N(R¹⁰)(R¹¹), -CH₂N(R¹²)C(O)R¹³, -CH₂S(O)₂R¹³, and -CH₂S(O)₂N(R¹⁰)(R¹¹), wherein C₁₋₆alkyl, C₁₋₆haloalkyl, C₂₋₆alkenyl, C₂₋₆alkynyl, C₃₋₆cycloalkyl, -CH₂-C₃₋₆cycloalkyl, C₂₋₉heterocycloalkyl, -CH₂-C₂₋₉heterocycloalkyl, C₆₋₁₀aryl, -CH₂-C₆₋₁₀aryl, C₁₋₉heteroaryl, -CH₂-C₁₋₉heteroaryl are optionally substituted with one, two, or three groups selected from halogen, -CN, C₁₋₆alkyl, C₁₋₆haloalkyl, C₃₋₆cycloalkyl, C₂₋₉heterocycloalkyl, C₆₋₁₀aryl, C₁₋₉heteroaryl, -OR¹⁰, and -N(R¹⁰)(R¹¹);

each R¹⁰ is independently selected from hydrogen, C₁₋₆alkyl, C₁₋₆haloalkyl, C₂₋₆alkenyl, C₂₋₆alkynyl, C₃₋₆cycloalkyl, C₂₋₉heterocycloalkyl, C₆₋₁₀aryl, and C₁₋₉heteroaryl, wherein C₁₋₆alkyl, C₂₋₆alkenyl, C₂₋₆alkynyl, C₃₋₆cycloalkyl, C₂₋₉heterocycloalkyl, C₆₋₁₀aryl, and C₁₋₉heteroaryl are optionally substituted with one, two, or three groups selected from halogen, -CN, hydroxy, C₁₋₆alkyl, C₁₋₆haloalkyl, C₁₋₆alkoxy, C₃₋₆cycloalkyl, C₂₋₉heterocycloalkyl, C₆₋₁₀aryl, and C₁₋₉heteroaryl;

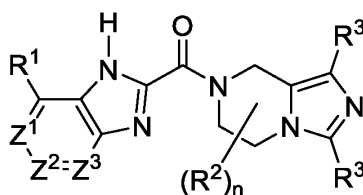
each R¹¹ is independently selected from hydrogen, C₁₋₆alkyl, and C₁₋₆haloalkyl;

each R¹² is independently selected from hydrogen, C₁₋₆alkyl, and C₁₋₆haloalkyl;

each R¹³ is independently selected C₁₋₆alkyl, C₂₋₆alkenyl, C₂₋₆alkynyl, C₃₋₆cycloalkyl, C₂₋₉heterocycloalkyl, C₆₋₁₀aryl, and C₁₋₉heteroaryl, wherein C₁₋₆alkyl, C₂₋₆alkenyl, C₂₋₆alkynyl, C₃₋₆cycloalkyl, C₂₋₉heterocycloalkyl, C₆₋₁₀aryl, and C₁₋₉heteroaryl are optionally substituted with one, two, or three groups selected from halogen, -CN, hydroxy, C₁₋₆alkyl, C₁₋₆haloalkyl, C₁₋₆alkoxy, C₃₋₆cycloalkyl, C₂₋₉heterocycloalkyl, C₆₋₁₀aryl, and C₁₋₉heteroaryl; and

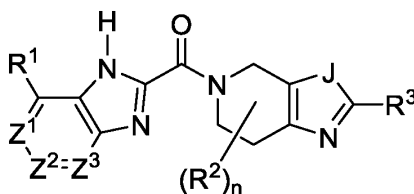
n is 0, 1, 2, 3, or 4.

6. The compound of claim 5, or a pharmaceutically acceptable salt or solvate thereof, having the structure of Formula (IIIa):



Formula (IIIa).

7. A compound of Formula (IV), or a pharmaceutically acceptable salt or solvate thereof:



Formula (IV);

wherein:

Z¹, Z², and Z³ are each independently C(R⁴) or N, wherein at least one of Z¹, Z², and Z³ is C(R⁴);

J is O or S;

R¹ is selected from hydrogen, halogen, -CN, -OR¹⁰, -SR¹⁰, -N(R¹⁰)(R¹¹), C₁₋₆alkyl, C₁₋₆haloalkyl, C₂₋₆alkenyl, C₂₋₆alkynyl, C₃₋₆cycloalkyl, C₂₋₉heterocycloalkyl, C₆₋₁₀aryl, and C₁₋₉heteroaryl, wherein C₁₋₆alkyl, C₁₋₆haloalkyl, C₂₋₆alkenyl, C₂₋₆alkynyl, C₃₋₆cycloalkyl, C₂₋₉heterocycloalkyl, C₆₋₁₀aryl, and C₁₋₉heteroaryl are optionally substituted with 1-5 R^{5a} groups;

each R² is independently selected from halogen, -CN, -OR¹⁰, -SR¹⁰, -N(R¹⁰)(R¹¹), C₁₋₆alkyl, C₁₋₆haloalkyl, C₂₋₆alkenyl, C₂₋₆alkynyl, C₃₋₆cycloalkyl, C₂₋₉heterocycloalkyl, C₆₋₁₀aryl, and C₁₋₉heteroaryl, wherein C₁₋₆alkyl, C₁₋₆haloalkyl, C₂₋₆alkenyl, C₂₋₆alkynyl, C₃₋₆cycloalkyl, C₂₋₉heterocycloalkyl, C₆₋₁₀aryl, and C₁₋₉heteroaryl are optionally substituted with 1-5 R^{5b} groups;

R³ is selected from hydrogen, halogen, -CN, -SR¹⁰, -N(R¹⁰)(R¹¹), C₁₋₆alkyl, C₁₋₆haloalkyl, C₁₋₆alkoxy, C₂₋₆alkenyl, C₂₋₆alkynyl, C₃₋₆cycloalkyl, C₂₋₉heterocycloalkyl, C₆₋₁₀aryl, and C₁₋₉heteroaryl, wherein C₁₋₆alkyl, C₁₋₆haloalkyl, C₁₋₆alkoxy, C₂₋₆alkenyl, C₂₋₆alkynyl, C₃₋₆cycloalkyl, C₂₋₉heterocycloalkyl, C₆₋₁₀aryl, and C₁₋₉heteroaryl are optionally substituted with 1-5 R^{5c} groups;

each R⁴ is independently selected from hydrogen, halogen, -CN, -OR¹⁰, -SR¹⁰, -N(R¹⁰)(R¹¹), C₁₋₆alkyl, C₁₋₆haloalkyl, C₂₋₆alkenyl, C₂₋₆alkynyl, C₃₋₆cycloalkyl, C₂₋₉heterocycloalkyl, C₆₋₁₀aryl, and C₁₋₉heteroaryl, wherein C₁₋₆alkyl, C₁₋₆haloalkyl, C₂₋₆alkenyl, C₂₋₆alkynyl, C₃₋₆cycloalkyl, C₂₋₉heterocycloalkyl, C₆₋₁₀aryl, and C₁₋₉heteroaryl are optionally substituted with 1-5 R^{5d} groups;

each R^{5a}, R^{5b}, R^{5c}, and R^{5d} is each independently selected from halogen, oxo, -CN, C₁₋₆alkyl, C₁₋₆haloalkyl, C₂₋₆alkenyl, C₂₋₆alkynyl, C₃₋₆cycloalkyl, -CH₂-C₃₋₆cycloalkyl, C₂₋₉heterocycloalkyl, -CH₂-C₂₋₉heterocycloalkyl, C₆₋₁₀aryl, -CH₂-C₆₋₁₀aryl, C₁₋₉heteroaryl, -CH₂-C₁₋₉heteroaryl, -OR¹⁰, -SR¹⁰, -N(R¹⁰)(R¹¹), -C(O)OR¹⁰, -OC(O)N(R¹⁰)(R¹¹), -N(R¹²)C(O)N(R¹⁰)(R¹¹), -N(R¹²)C(O)OR¹³, -N(R¹²)S(O)₂R¹³, -C(O)R¹³, -S(O)R¹³, -OC(O)R¹³, -C(O)N(R¹⁰)(R¹¹), -C(O)C(O)N(R¹⁰)(R¹¹), -N(R¹²)C(O)R¹³, -S(O)₂R¹³, -S(O)₂N(R¹⁰)(R¹¹), -S(=O)(=NH)N(R¹⁰)(R¹¹), -C(=NOR¹¹)R¹³, -CH₂C(O)N(R¹⁰)(R¹¹), -CH₂N(R¹²)C(O)R¹³, -CH₂S(O)₂R¹³, and -CH₂S(O)₂N(R¹⁰)(R¹¹), wherein C₁₋₆alkyl, C₁₋₆haloalkyl, C₂₋₆alkenyl, C₂₋₆alkynyl, C₃₋₆cycloalkyl, -CH₂-C₃₋₆cycloalkyl, C₂₋₉heterocycloalkyl, -CH₂-C₂₋₉heterocycloalkyl, C₆₋₁₀aryl, -CH₂-C₆₋₁₀aryl, C₁₋₉heteroaryl, -CH₂-C₁₋₉heteroaryl are optionally substituted with one, two, or three groups selected from halogen, -CN, C₁₋₆alkyl, C₁₋₆haloalkyl, C₃₋₆cycloalkyl, C₂₋₉heterocycloalkyl, C₆₋₁₀aryl, C₁₋₉heteroaryl, -OR¹⁰, and -N(R¹⁰)(R¹¹);

each R¹⁰ is independently selected from hydrogen, C₁₋₆alkyl, C₁₋₆ haloalkyl, C₂₋₆alkenyl, C₂₋₆alkynyl, C₃₋₆cycloalkyl, C₂₋₉heterocycloalkyl, C₆₋₁₀aryl, and C₁₋₉heteroaryl, wherein C₁₋₆alkyl, C₂₋₆alkenyl, C₂₋₆alkynyl, C₃₋₆cycloalkyl, C₂₋₉heterocycloalkyl, C₆₋₁₀aryl, and C₁₋₉heteroaryl are optionally substituted with one, two, or three groups selected from halogen, -CN, hydroxy, C₁₋₆alkyl, C₁₋₆haloalkyl, C₁₋₆alkoxy, C₃₋₆cycloalkyl, C₂₋₉heterocycloalkyl, C₆₋₁₀aryl, and C₁₋₉heteroaryl;

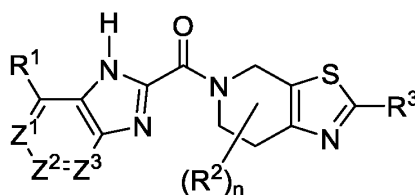
each R¹¹ is independently selected from hydrogen, C₁₋₆alkyl, and C₁₋₆haloalkyl;

each R¹² is independently selected from hydrogen, C₁₋₆alkyl, and C₁₋₆haloalkyl;

each R¹³ is independently selected C₁₋₆alkyl, C₂₋₆alkenyl, C₂₋₆alkynyl, C₃₋₆cycloalkyl, C₂₋₉heterocycloalkyl, C₆₋₁₀aryl, and C₁₋₉heteroaryl, wherein C₁₋₆alkyl, C₂₋₆alkenyl, C₂₋₆alkynyl, C₃₋₆cycloalkyl, C₂₋₉heterocycloalkyl, C₆₋₁₀aryl, and C₁₋₉heteroaryl are optionally substituted with one, two, or three groups selected from halogen, -CN, hydroxy, C₁₋₆alkyl, C₁₋₆haloalkyl, C₁₋₆alkoxy, C₃₋₆cycloalkyl, C₂₋₉heterocycloalkyl, C₆₋₁₀aryl, and C₁₋₉heteroaryl; and

n is 0, 1, 2, 3, or 4.

8. The compound of claim 7, or a pharmaceutically acceptable salt or solvate thereof, having the structure of Formula (IVa):

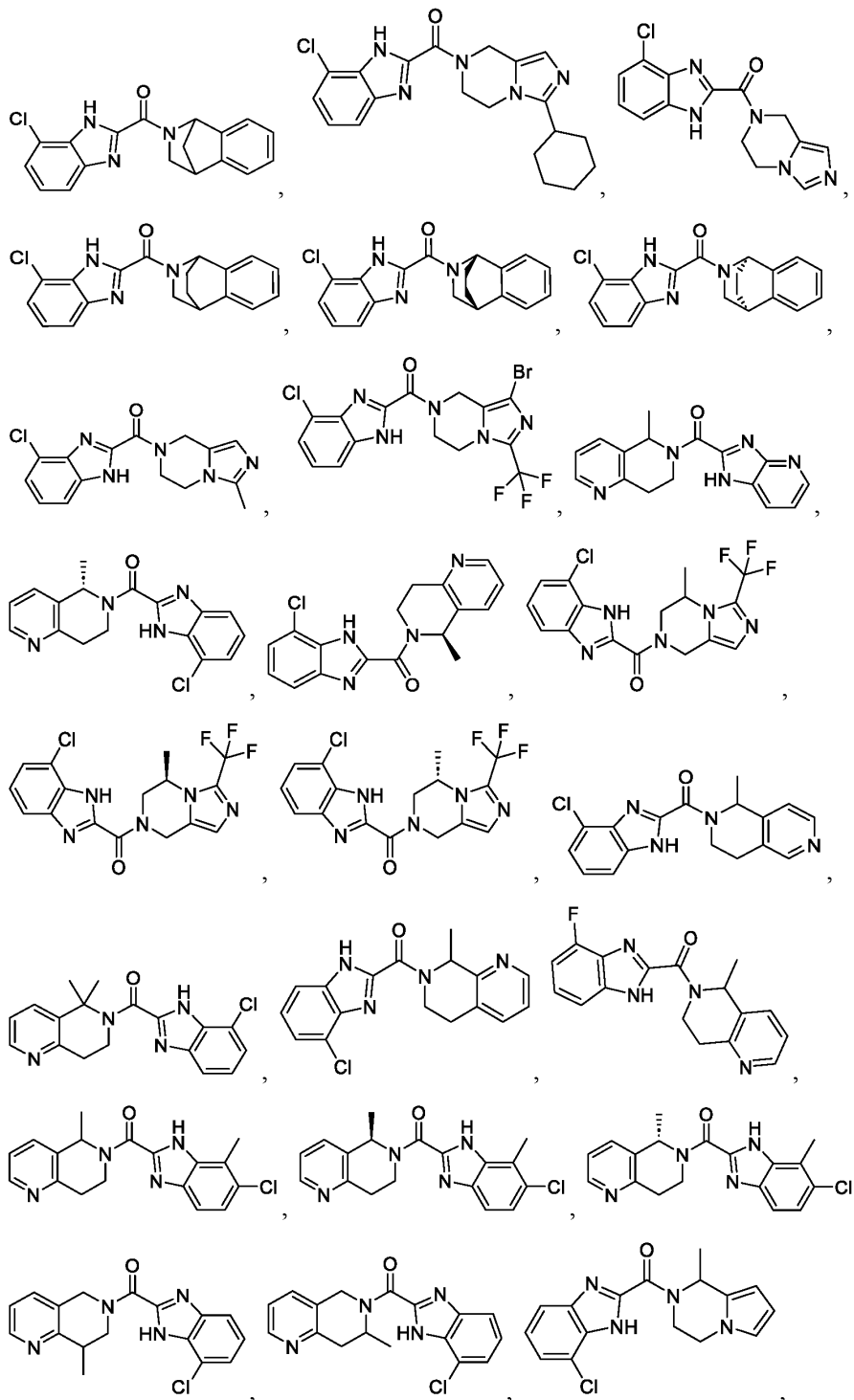


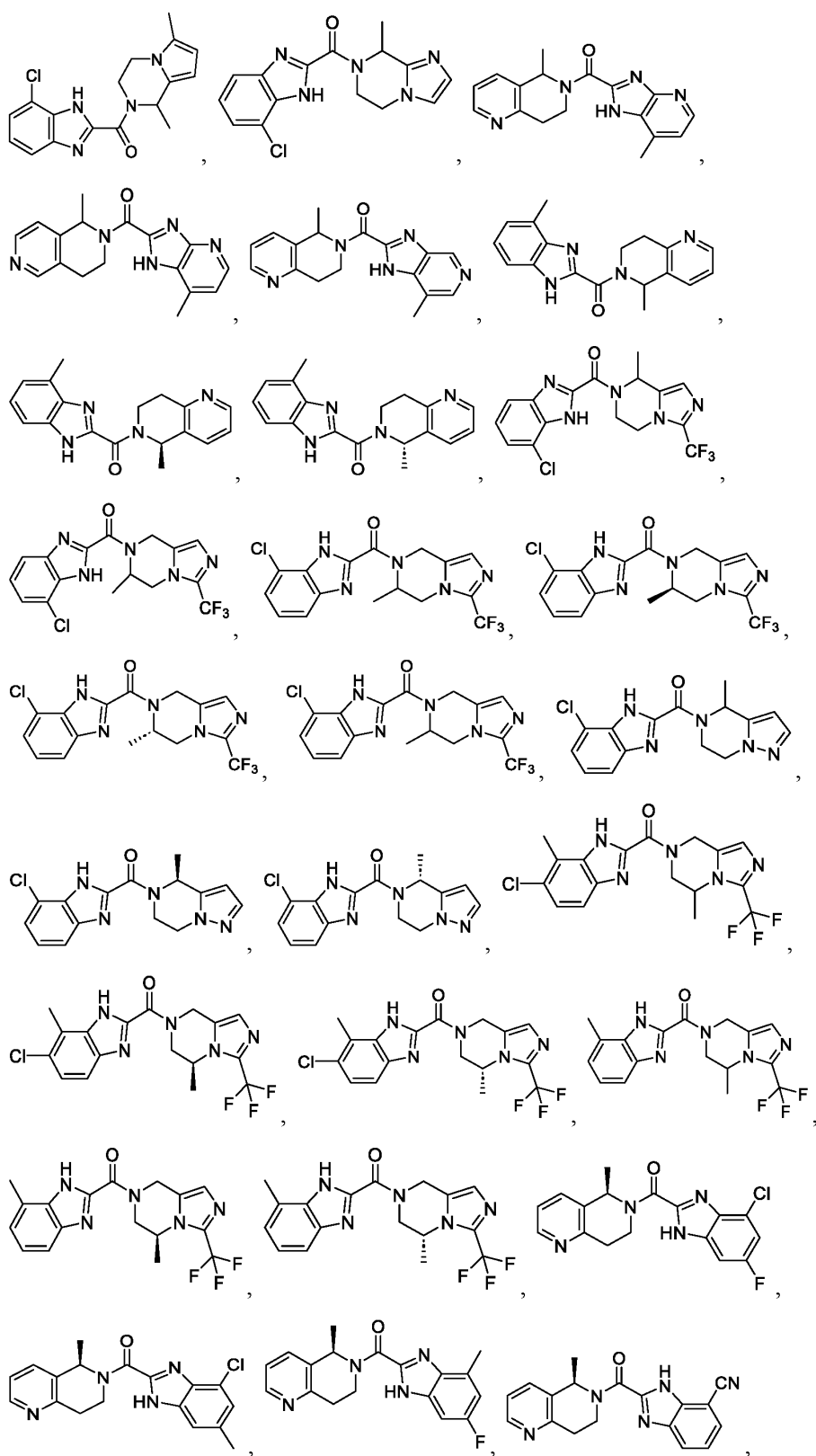
Formula (IVa).

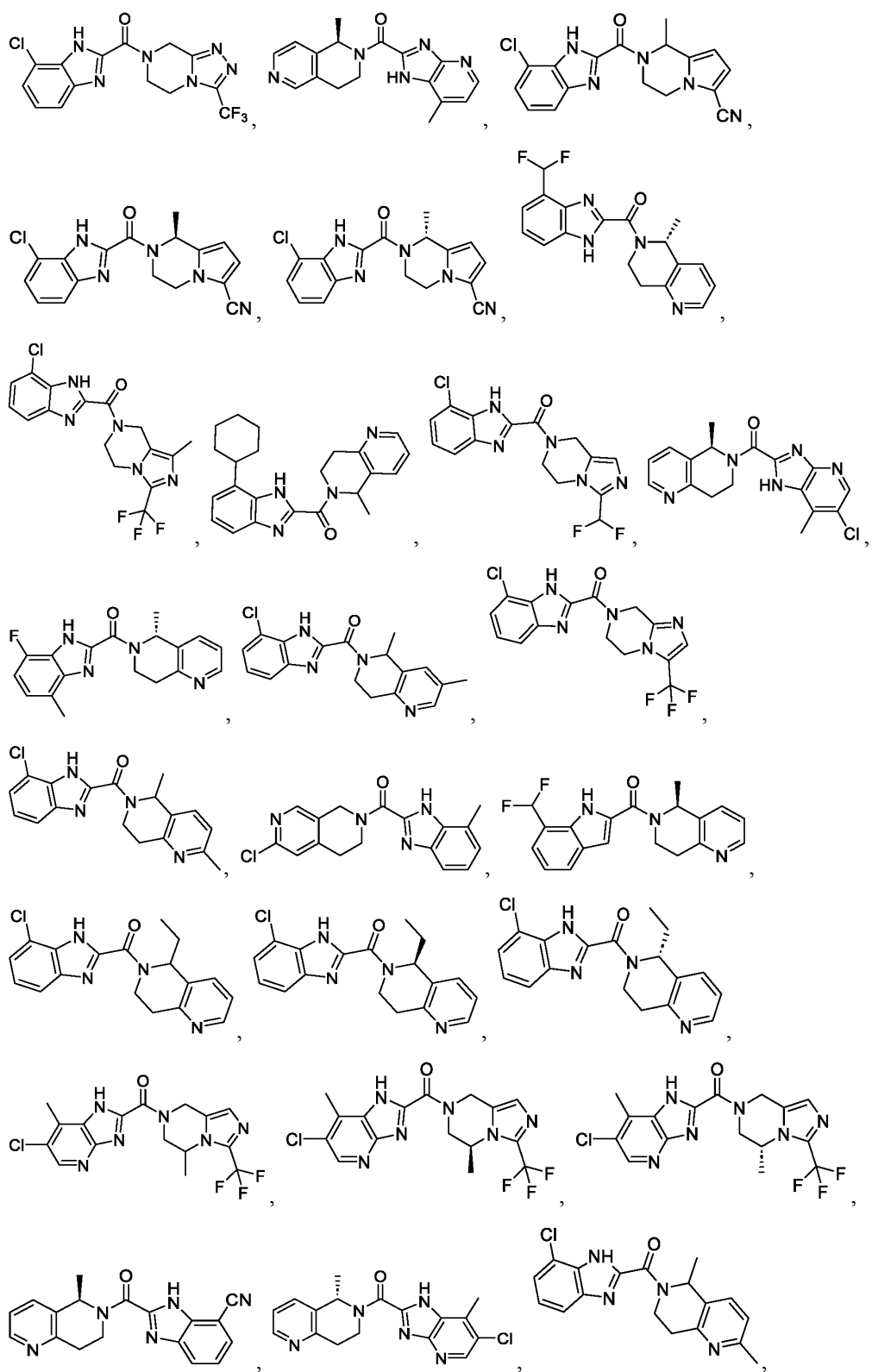
9. The compound of any one of claims 1-8, or a pharmaceutically acceptable salt or solvate thereof, wherein each R³ is independently selected from hydrogen, halogen, -CN, -N(R¹⁰)(R¹¹), C₁₋₆alkyl, C₁₋₆haloalkyl, C₁₋₆alkoxy, and C₃₋₆cycloalkyl, wherein C₁₋₆alkyl, C₁₋₆haloalkyl, C₁₋₆alkoxy, and C₃₋₆cycloalkyl are optionally substituted with 1-5 R^{5c} groups.
10. The compound of any one of claims 1-9, or a pharmaceutically acceptable salt or solvate thereof, wherein each R³ is independently selected from hydrogen, halogen, -CN, C₁₋₆alkyl, C₁₋₆haloalkyl, and C₁₋₆alkoxy, wherein C₁₋₆alkyl, C₁₋₆haloalkyl, and C₁₋₆alkoxy are optionally substituted with 1-5 R^{5c} groups.
11. The compound of any one of claims 1-10, or a pharmaceutically acceptable salt or solvate thereof, wherein each R³ is independently selected from hydrogen, halogen, -CN, C₁₋₆alkyl, C₁₋₆haloalkyl, and C₁₋₆alkoxy, wherein C₁₋₆alkyl, C₁₋₆haloalkyl, and C₁₋₆alkoxy are optionally substituted with 1-3 R^{5c} groups.
12. The compound of any one of claims 1-11, or a pharmaceutically acceptable salt or solvate thereof, wherein each R³ is independently selected from hydrogen, halogen, -CN, unsubstituted C₁₋₆alkyl, -CF₃, and -OCH₃.
13. The compound of any one of claims 1-12, or a pharmaceutically acceptable salt or solvate thereof, wherein each R³ is independently selected from hydrogen, halogen, and -CH₃.
14. The compound of any one of claims 1-13, or a pharmaceutically acceptable salt or solvate thereof, wherein each R³ is hydrogen.
15. The compound of any one of claims 1-14, or a pharmaceutically acceptable salt or solvate thereof, wherein each R² is independently selected from -OR¹⁰, C₁₋₆alkyl, and C₁₋₆haloalkyl, wherein C₁₋₆alkyl and C₁₋₆haloalkyl are optionally substituted with 1-5 R^{5b} groups.
16. The compound of any one of claims 1-15, or a pharmaceutically acceptable salt or solvate thereof, wherein each R² is independently selected from unsubstituted C₁₋₆alkyl.

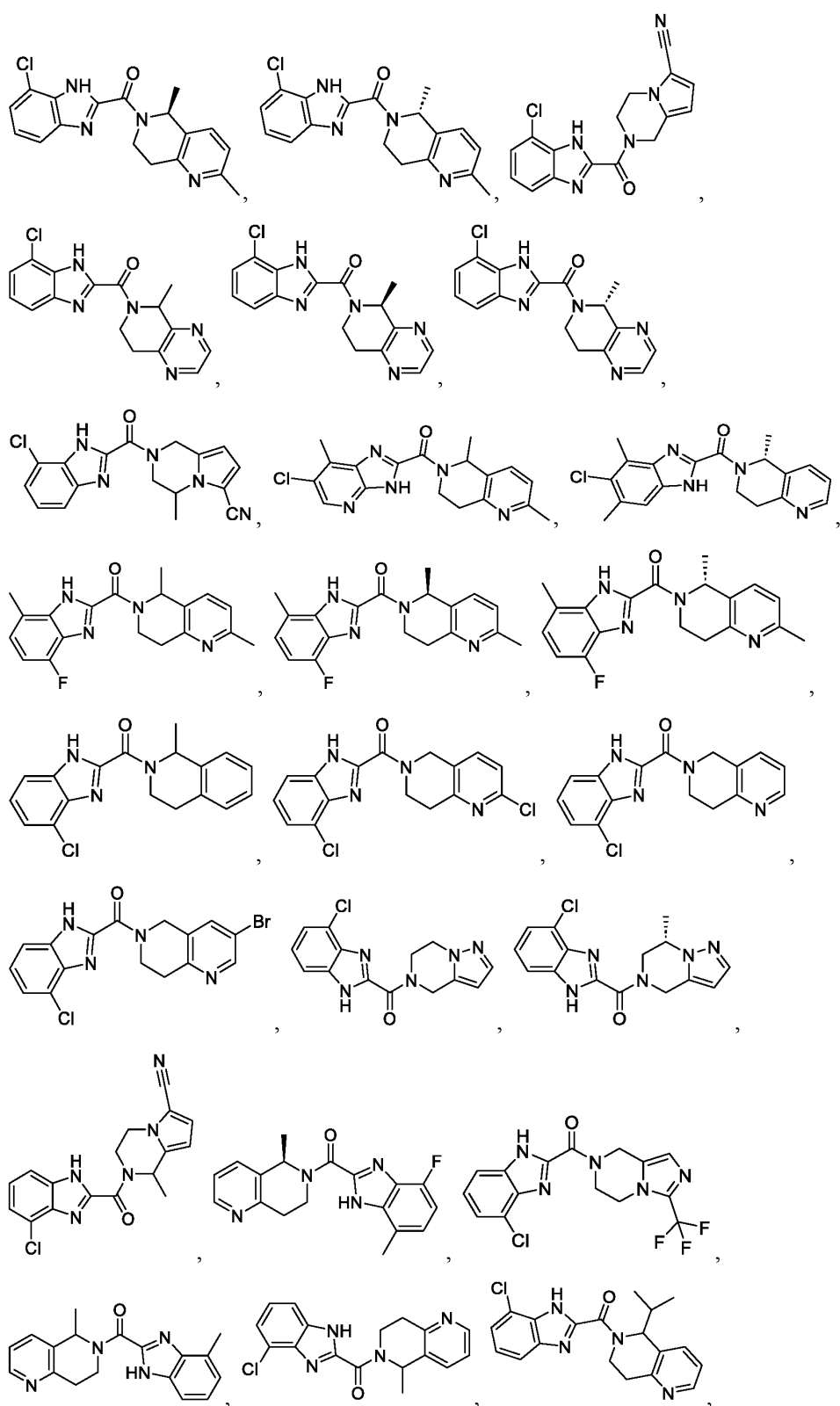
17. The compound of any one of claims 1-16, or a pharmaceutically acceptable salt or solvate thereof, wherein each R² is -CH₃.
18. The compound of any one of claims 1-17, or a pharmaceutically acceptable salt or solvate thereof, wherein n is 1.
19. The compound of any one of claims 1-17, or a pharmaceutically acceptable salt or solvate thereof, wherein n is 2.
20. The compound of any one of claims 1-14, or a pharmaceutically acceptable salt or solvate thereof, wherein n is 0.
21. The compound of any one of claims 1-20, or a pharmaceutically acceptable salt or solvate thereof, wherein R¹ is selected from halogen, -CN, -OR¹⁰, C₁₋₆alkyl, C₁₋₆haloalkyl, C₆₋₁₀aryl, and C₁₋₉heteroaryl, wherein C₁₋₆alkyl and C₁₋₆haloalkyl are optionally substituted with 1-5 R^{5a} groups.
22. The compound of any one of claims 1-21, or a pharmaceutically acceptable salt or solvate thereof, wherein R¹ is selected from halogen, -CN, -OR¹⁰, C₁₋₆alkyl, and C₁₋₆haloalkyl, wherein C₁₋₆alkyl and C₁₋₆haloalkyl are optionally substituted with 1-5 R^{5a} groups.
23. The compound of any one of claims 1-22, or a pharmaceutically acceptable salt or solvate thereof, wherein R¹ is selected from halogen, -CN, -OR¹⁰, unsubstituted C₁₋₆alkyl, and unsubstituted C₁₋₆haloalkyl.
24. The compound of any one of claims 1-23, or a pharmaceutically acceptable salt or solvate thereof, wherein R¹ is selected from halogen, -CN, -OH, -OCH₃, -CH₃, and -CF₃.
25. The compound of any one of claims 1-24, or a pharmaceutically acceptable salt or solvate thereof, wherein R¹ is halogen.
26. The compound of any one of claims 1-25, or a pharmaceutically acceptable salt or solvate thereof, wherein Z¹, Z², and Z³ are each independently C(R⁴).
27. The compound of any one of claims 1-26, or a pharmaceutically acceptable salt or solvate thereof, wherein each R⁴ is independently selected from hydrogen, halogen, -CN, -OR¹⁰, C₁₋₆alkyl, C₁₋₆haloalkyl, and C₃₋₆cycloalkyl, wherein C₁₋₆alkyl, C₁₋₆haloalkyl, and C₃₋₆cycloalkyl are optionally substituted with 1-5 R^{5d} groups.
28. The compound of any one of claims 1-27, or a pharmaceutically acceptable salt or solvate thereof, wherein each R⁴ is independently selected from hydrogen, halogen, and unsubstituted C₁₋₆alkyl.
29. The compound of any one of claims 1-28, or a pharmaceutically acceptable salt or solvate thereof, wherein each R⁴ is independently selected from hydrogen and halogen.

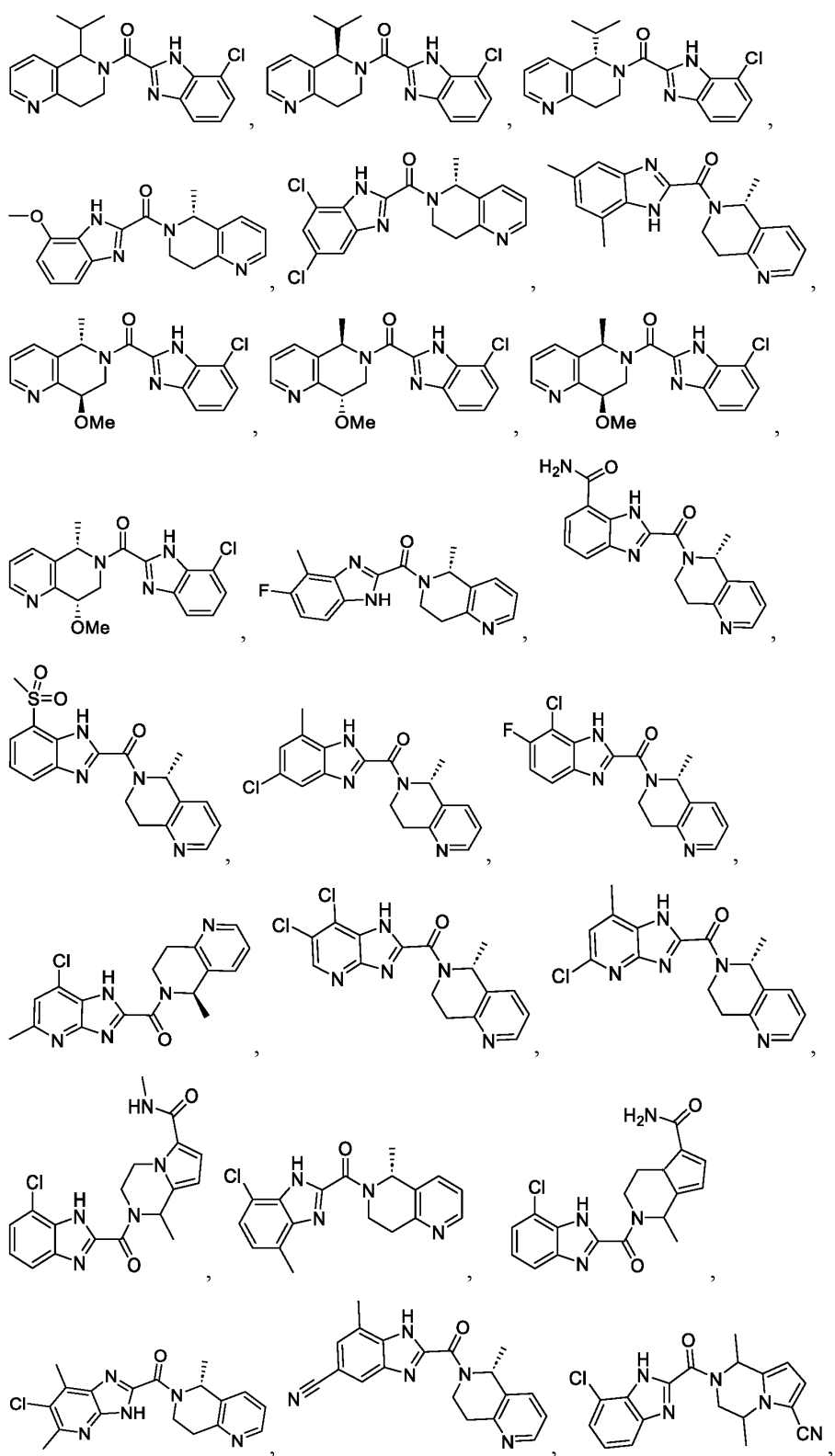
30. The compound of any one of claims 1-29, or a pharmaceutically acceptable salt or solvate thereof, wherein each R^4 is hydrogen.
31. A compound, or a pharmaceutically acceptable salt or solvate thereof, selected from:

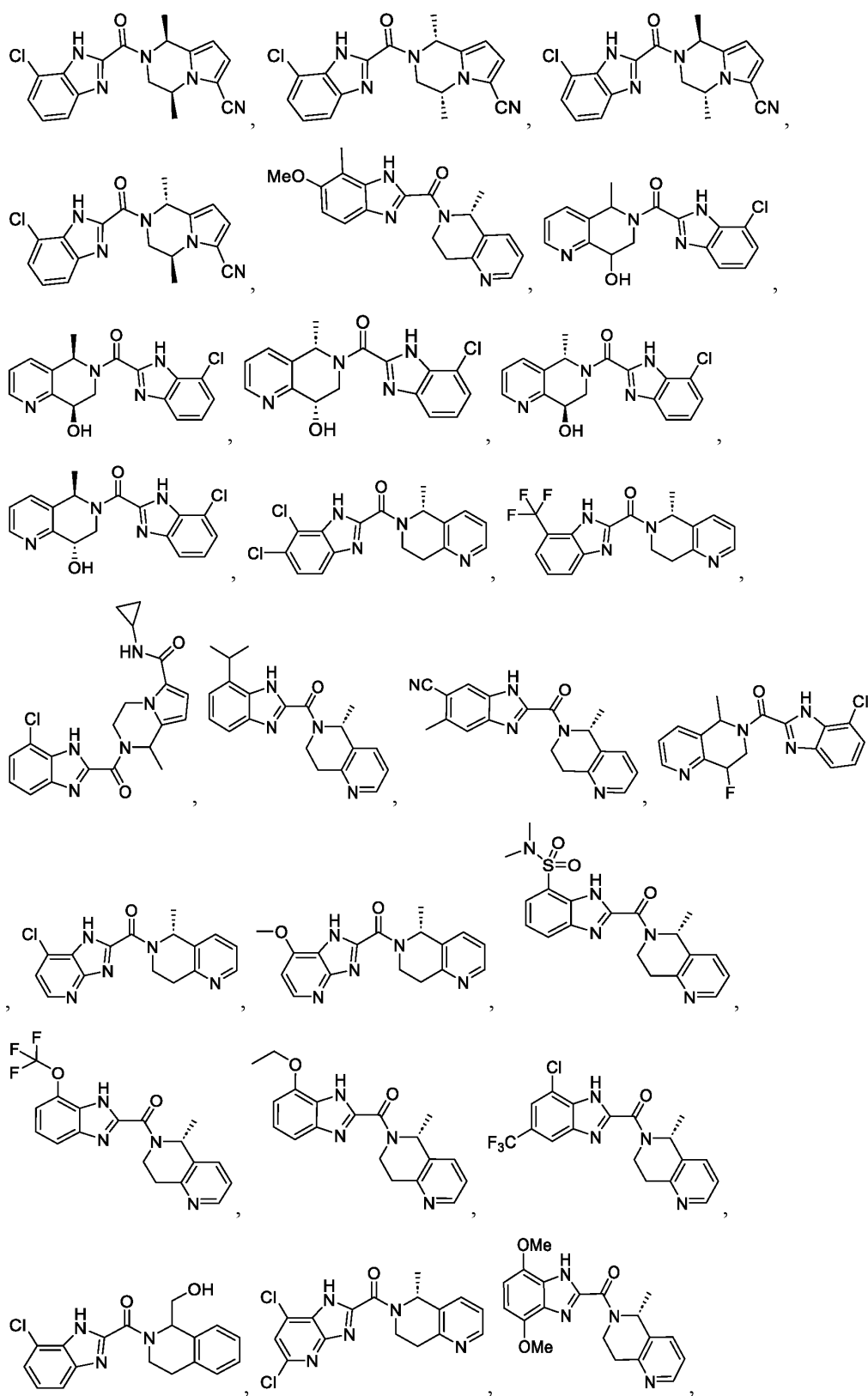


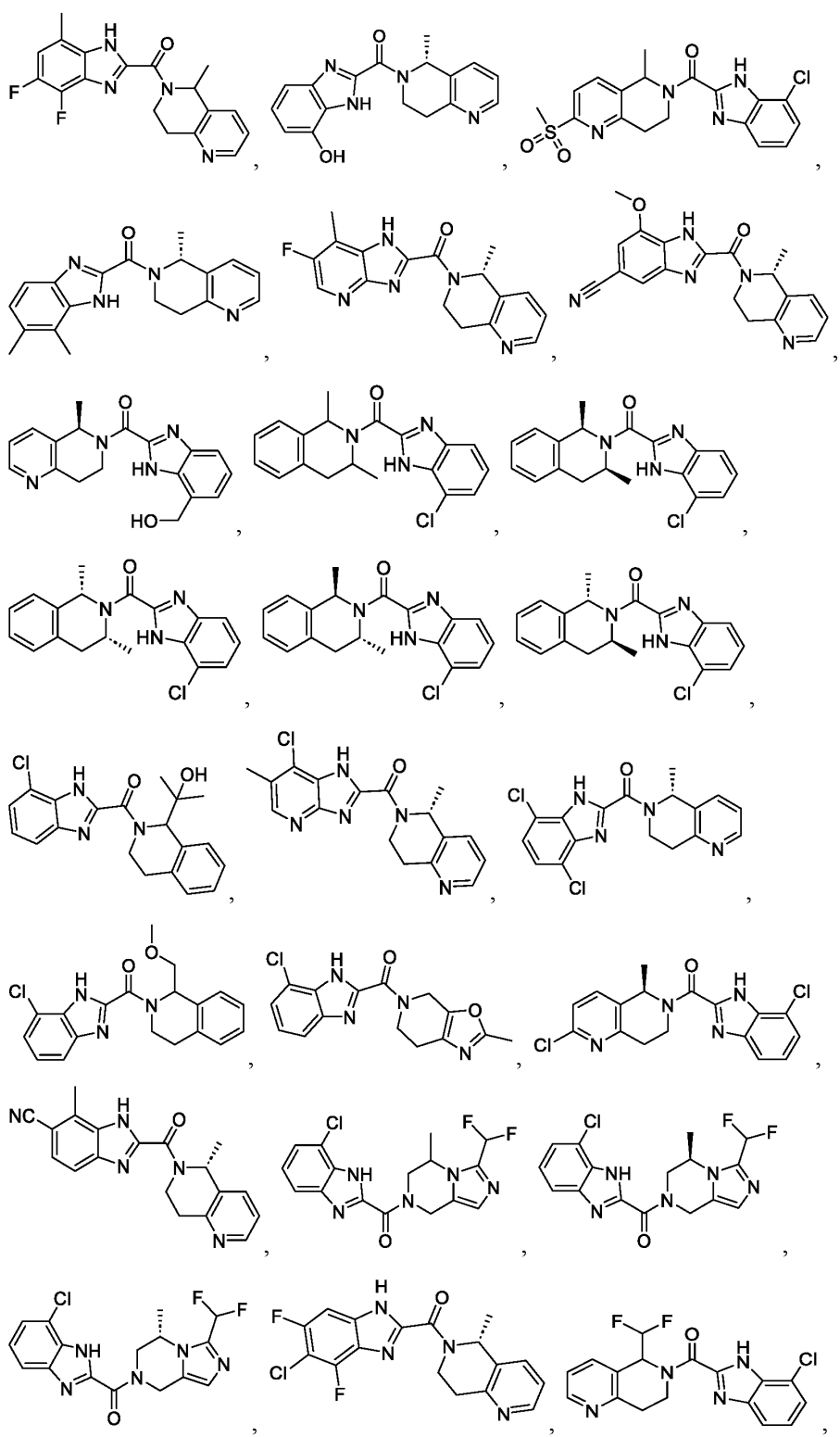


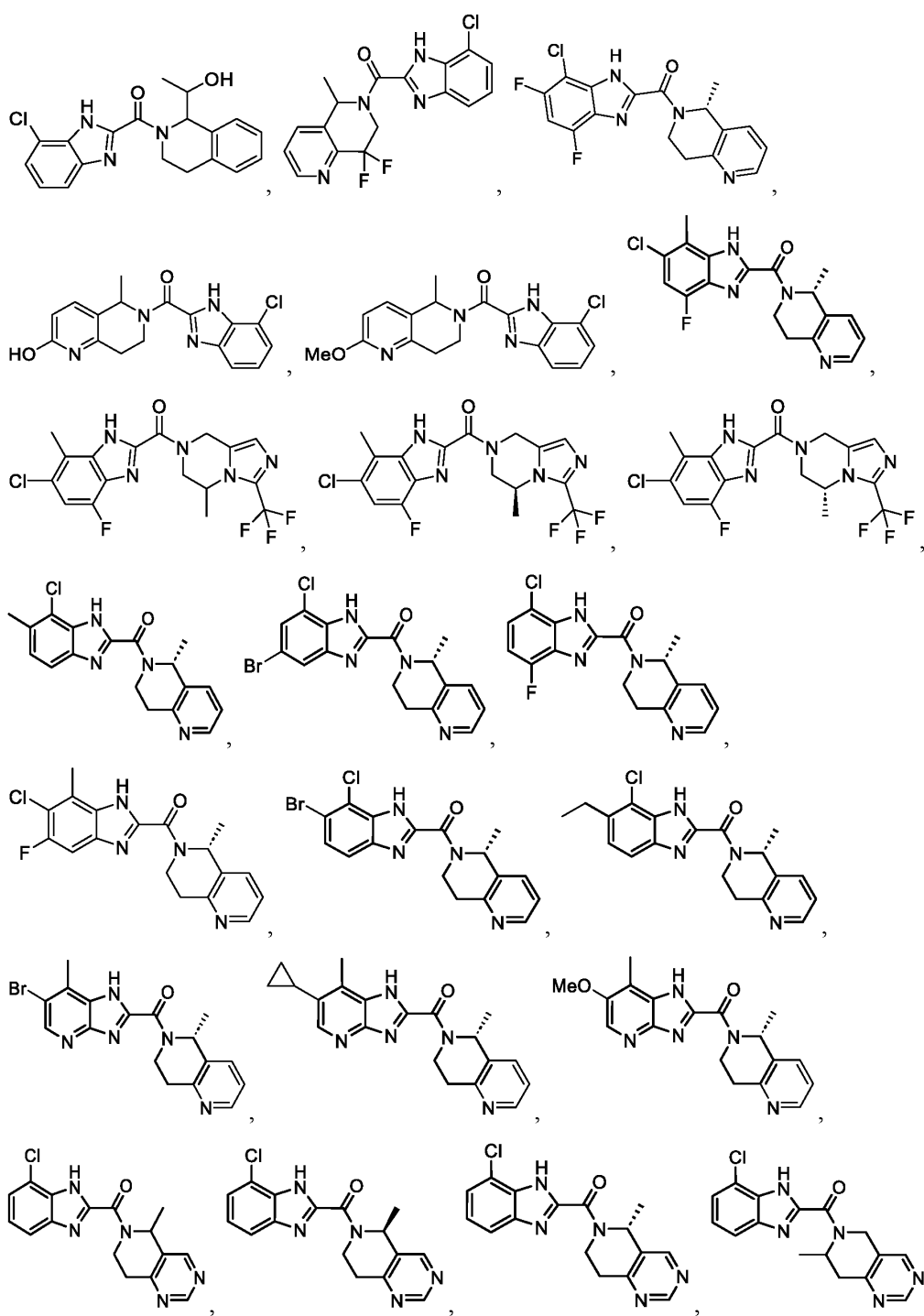


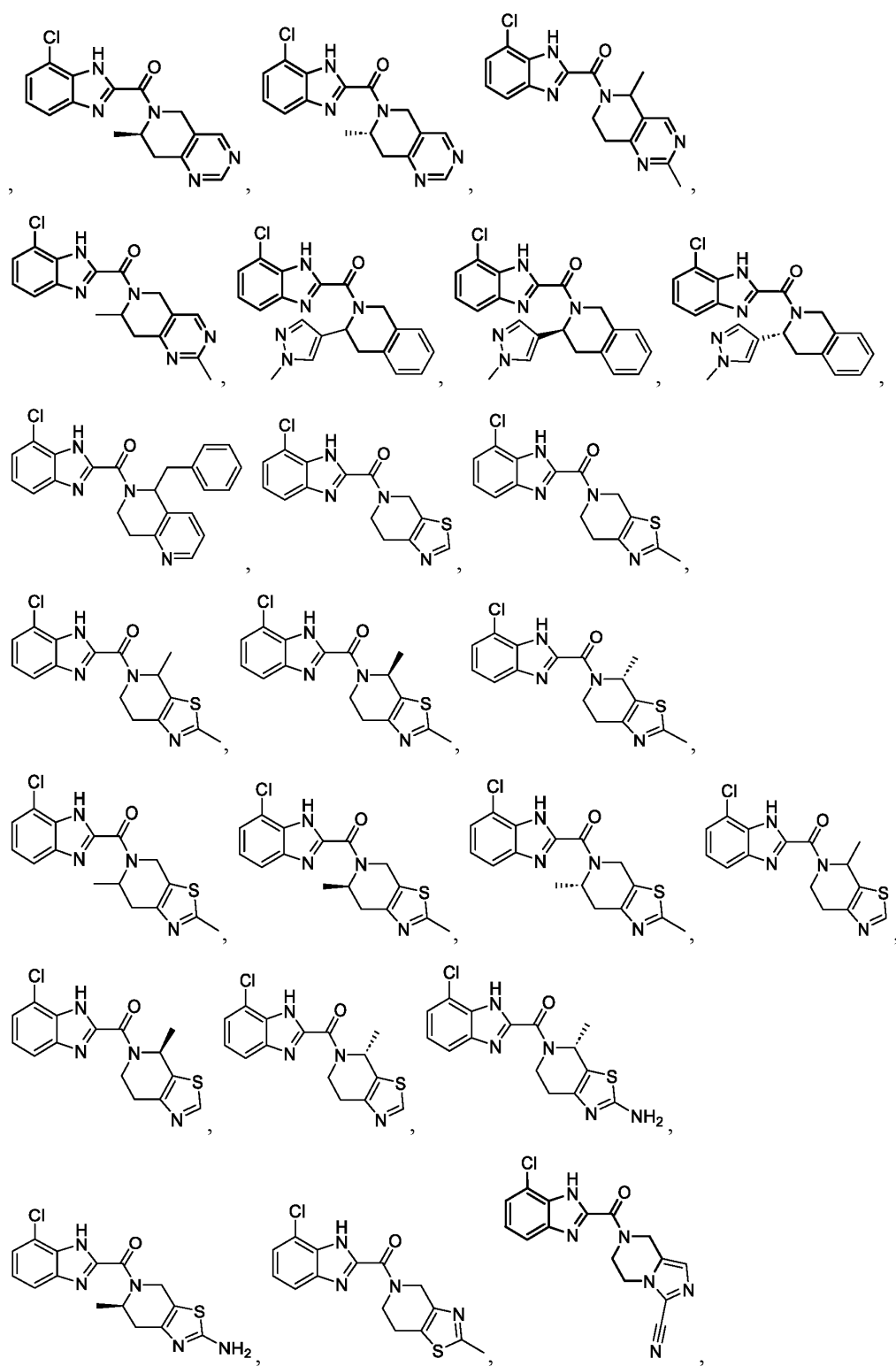


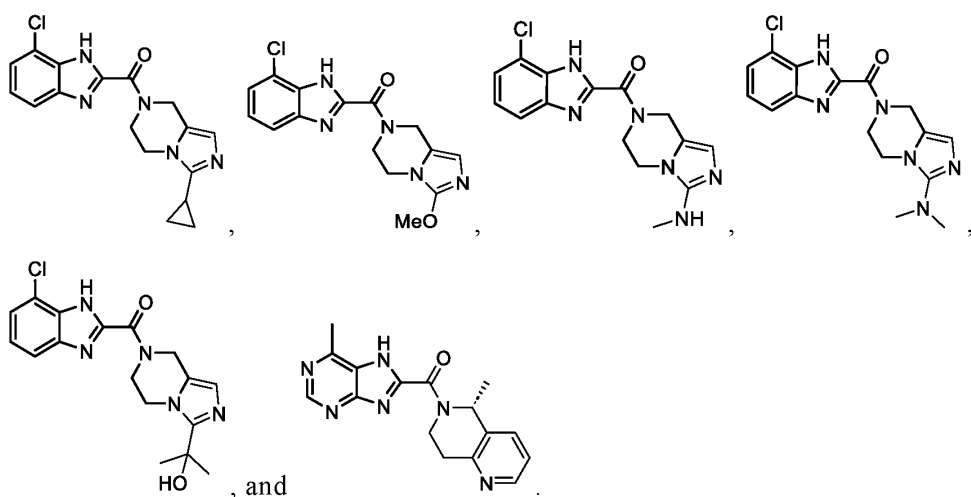




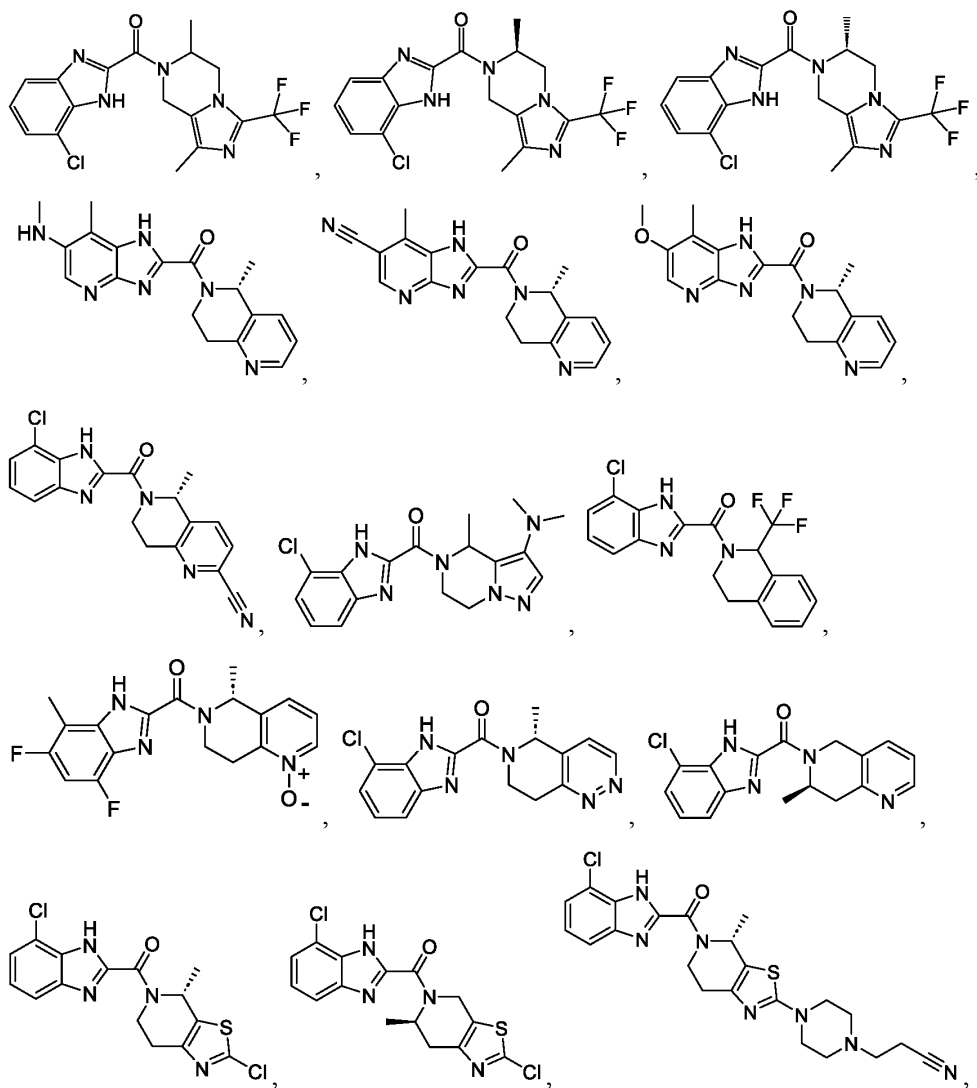


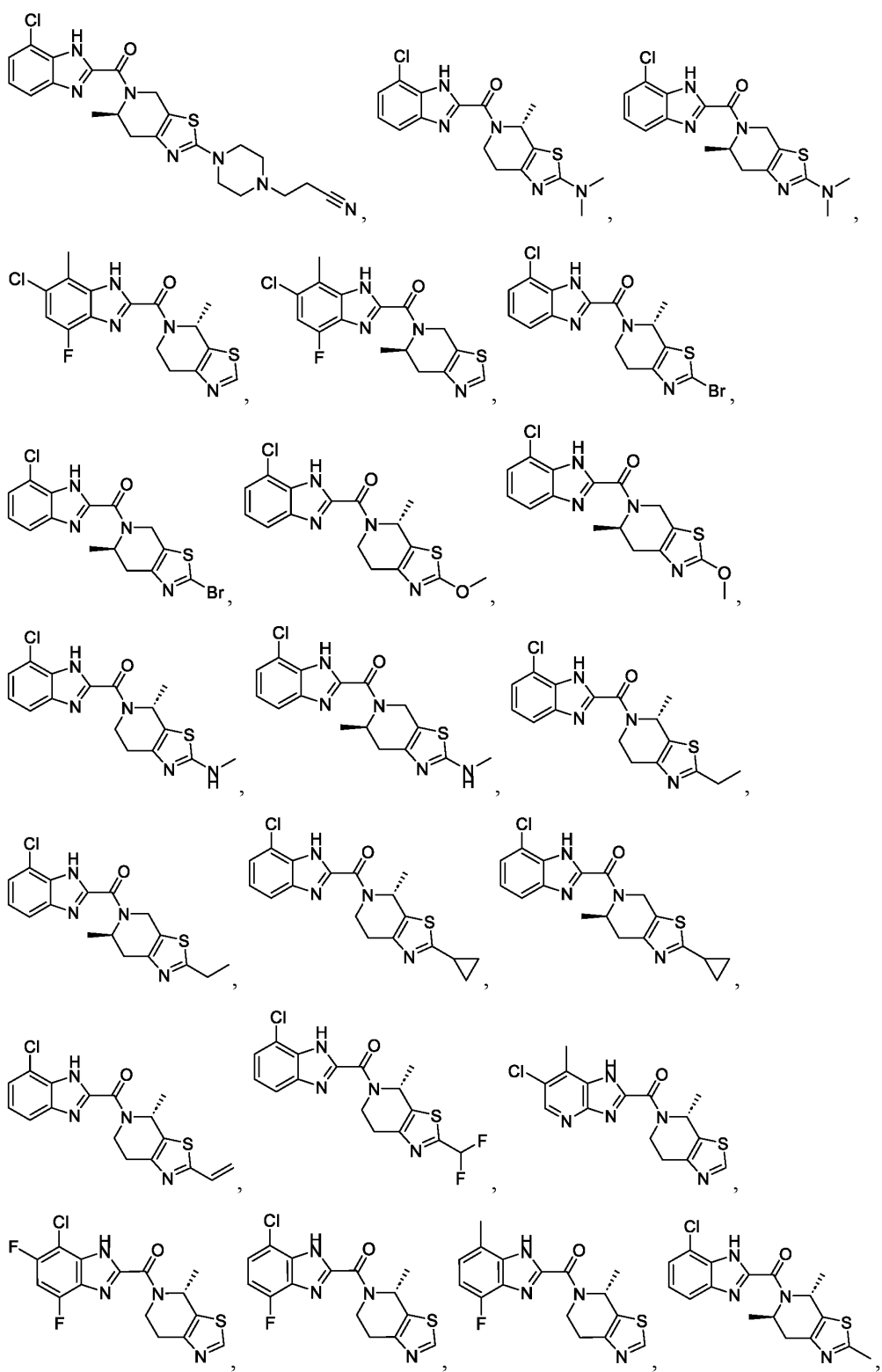


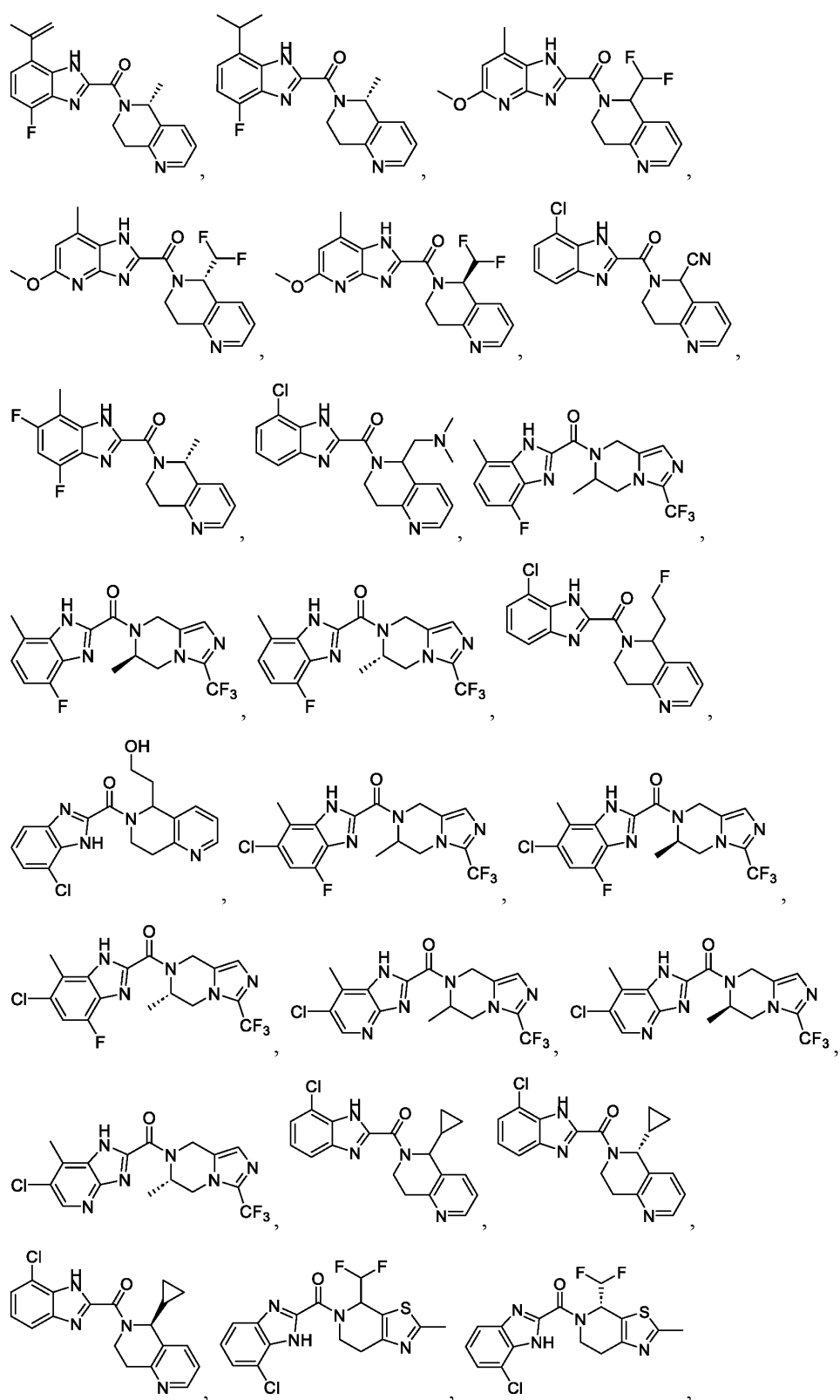


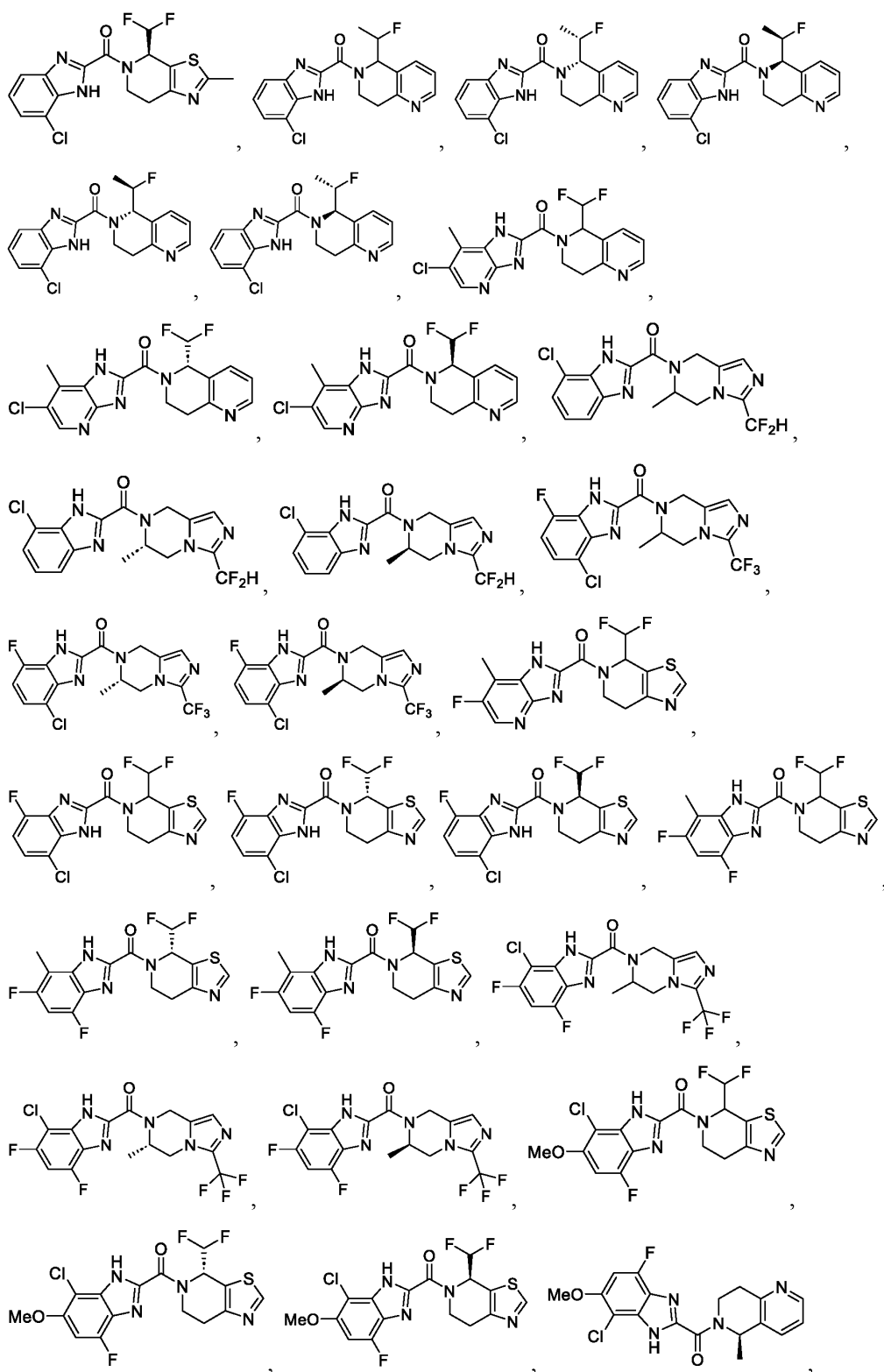


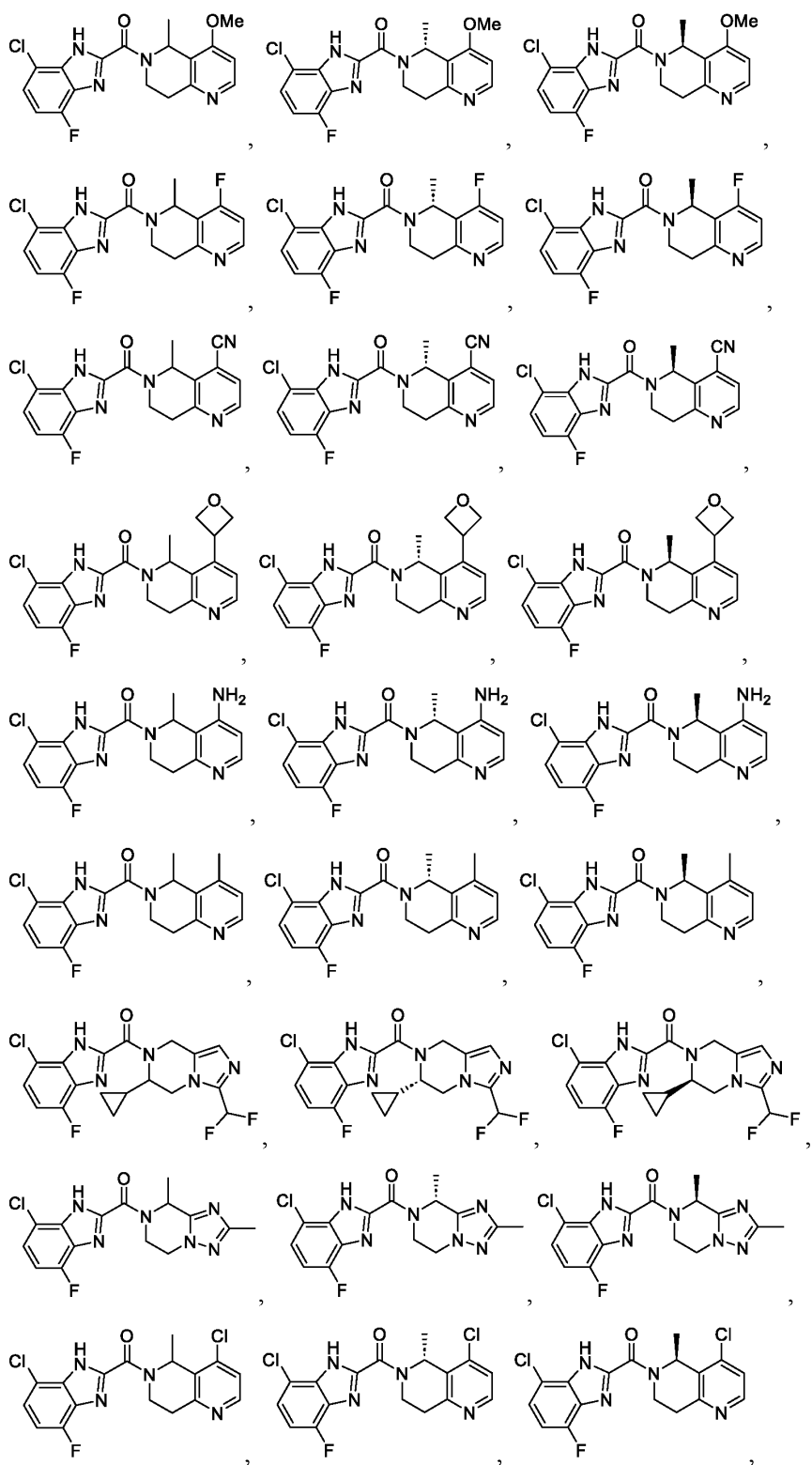
32. A compound, or a pharmaceutically acceptable salt or solvate thereof, selected from:

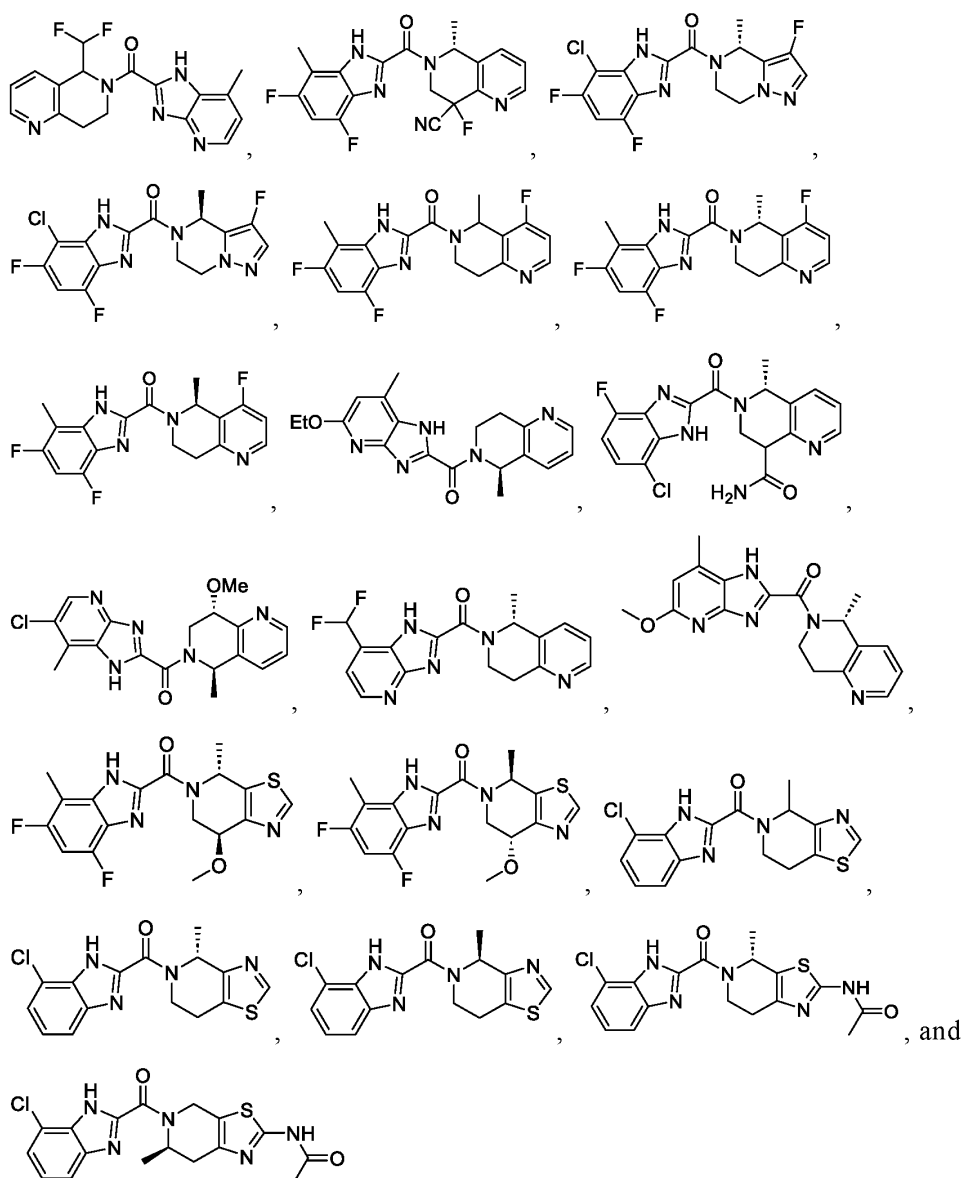












33. A pharmaceutical composition comprising a compound of any one of claims 1-32, or a pharmaceutically acceptable salt or solvate thereof, and at least one pharmaceutically acceptable excipient.
34. A method of treating autosomal dominant retinitis pigmentosa (adRP) in a subject in need thereof, comprising administering to the subject a compound of any one of claims 1-32, or a pharmaceutically acceptable salt or solvate.