INHIBITORS OF CYCLIN-DEPENDENT KINASES

CROSS REFERENCE TO RELATED APPLICATIONS

[0001] This application claims the benefit of U.S. Provisional Application No. 62/691,879, filed June 29, 2018, which is incorporated by reference in the disclosure of this application.

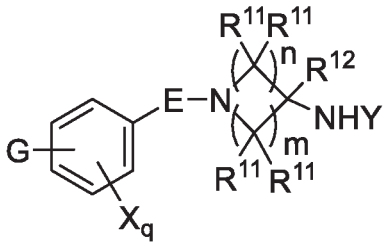
BACKGROUND

[0002] Cyclin-dependent kinases (CDKs) are a family of multifunctional enzymes that modify various protein substrates involved in cell cycle progression. Specifically, CDKs phosphorylate their substrates by transferring phosphate groups from ATP to specific stretches of amino acids in the substrates. The deregulation of CDKs is involved in the etiology of many human diseases, including cancers.

BRIEF SUMMARY OF THE INVENTION

[0003] Provided herein are inhibitors of cyclin-dependent kinases (CDKs), pharmaceutical compositions comprising said compounds, and methods for using said compounds for the treatment of diseases.

[0004] One embodiment provides a compound, or pharmaceutically acceptable salt or solvate thereof, having the structure of Formula (I):

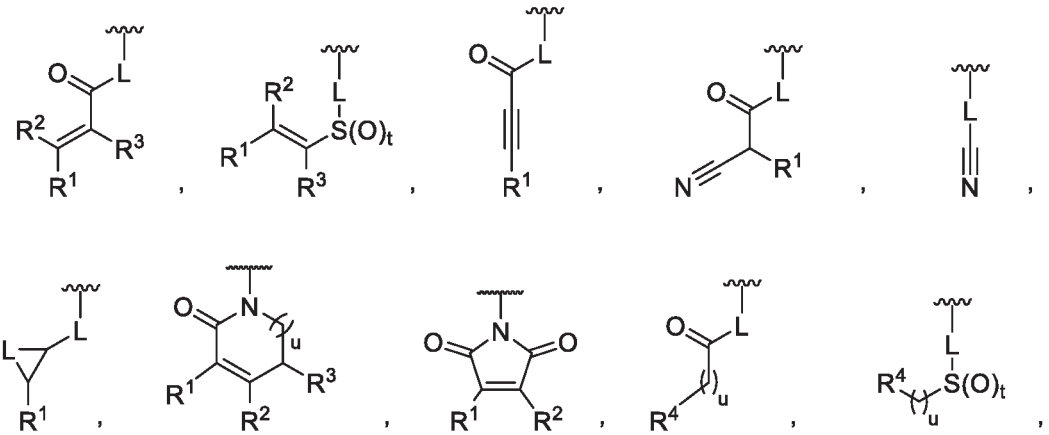


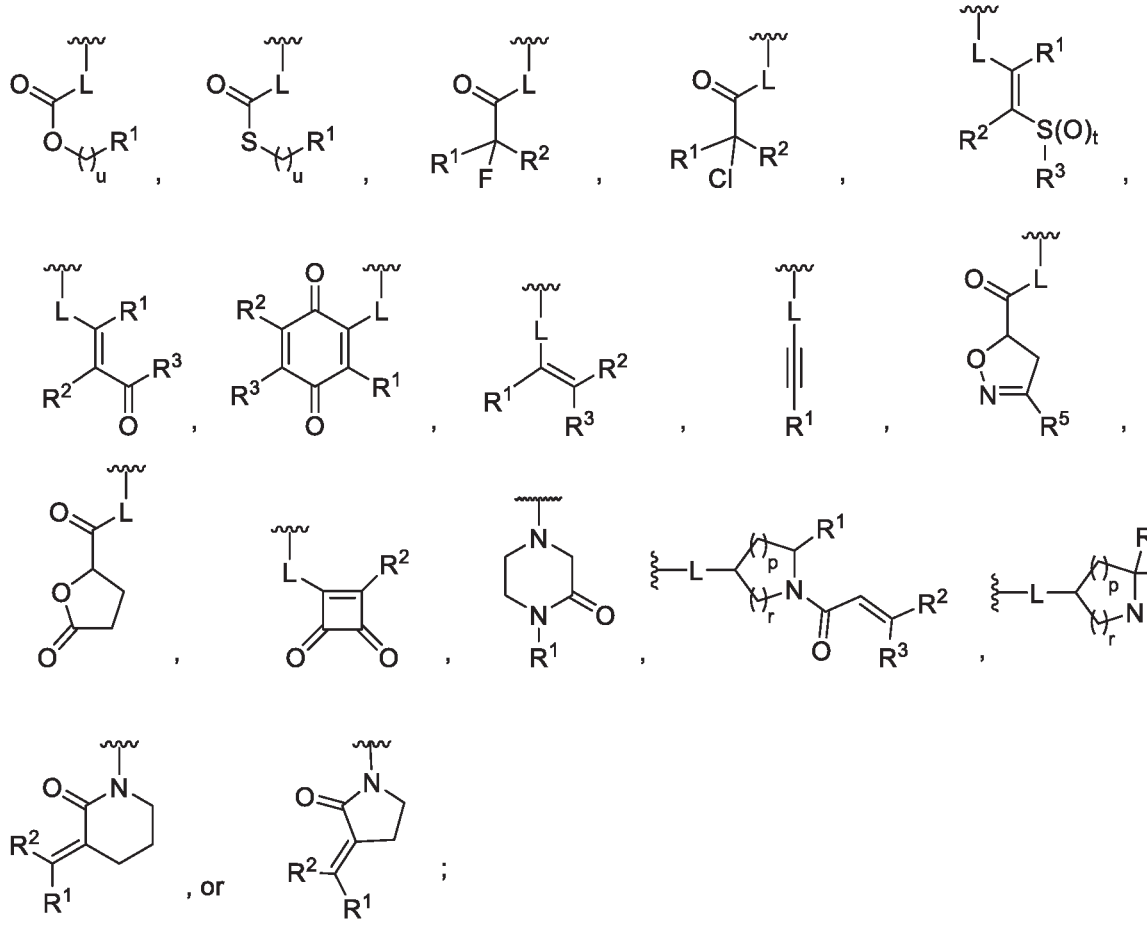
(I)

wherein,

E is selected from a bond, $-SO_2-$, $-C(O)-$, $-CH_2-$, $-CH(R^4)-$, or $-C(R^4)_2-$;

G is selected from a group having the structure:





wherein,

L is O, NH, N(optionally substituted C1-C4 alkyl), or -NH-CH_2-* wherein the * denotes the point of attachment to the phenyl ring;

t is 0, 1, or 2;

u is 1, or 2;

p is 0, 1, or 2;

r is 0, 1, or 2;

R^1 is selected from hydrogen, optionally substituted C1-C4 alkyl, or optionally substituted heterocyclylalkyl;

R^2 is selected from hydrogen, or optionally substituted C1-C4 alkyl;

R^3 is selected from hydrogen, -CN, or optionally substituted C1-C4 alkyl;

each R^4 is independently selected from optionally substituted C1-C4 alkyl, or optionally substituted heterocyclylalkyl;

R^5 is optionally substituted C1-C4 alkyl, or optionally substituted heterocyclylalkyl;

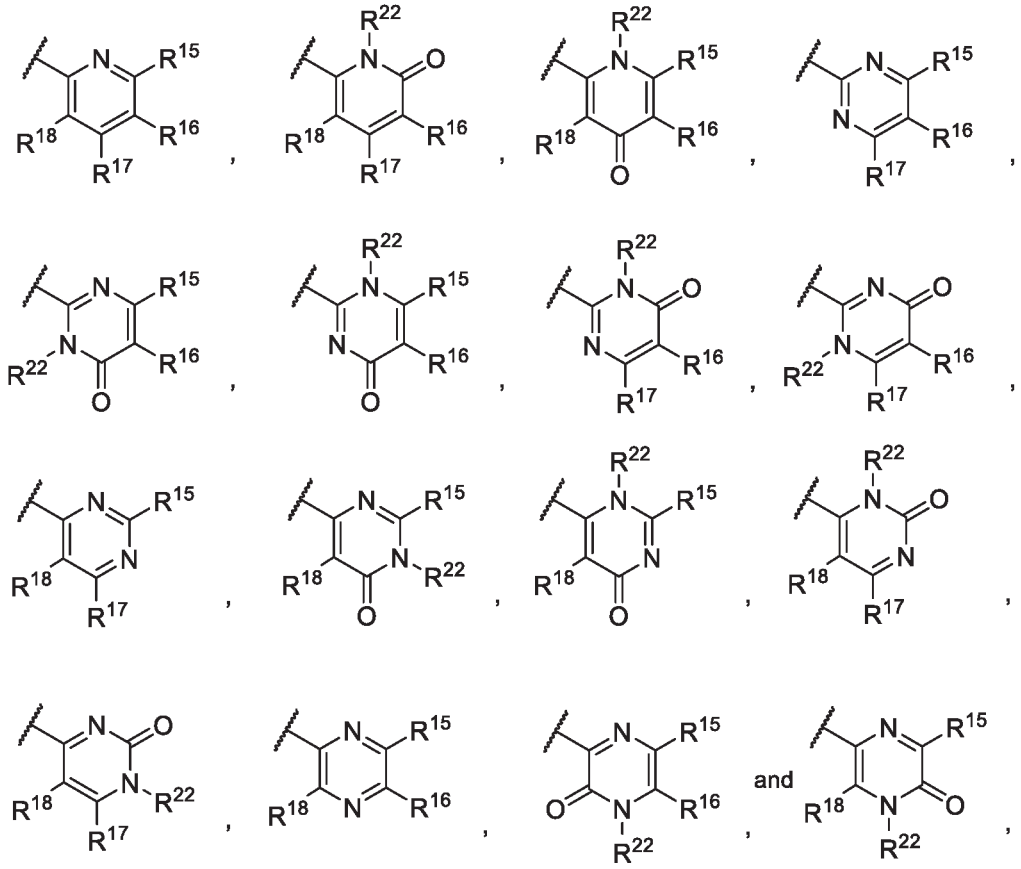
each R^{11} is independently hydrogen, halogen, optionally substituted C1-C6 alkyl, -OH, optionally substituted C1-C4 alkoxy, or two R^{11} groups on the same carbon atom form an oxo;

R^{12} is hydrogen or optionally substituted C1-C4 alkyl;

q is 0, 1, 2, or 3; n is 0, 1, 2, or 3; m is 0, 1, 2, or 3;

each X is independently halogen, optionally substituted C1-C4 alkyl, optionally substituted C1-C4 alkoxy, optionally substituted aminoalkyl, optionally substituted cycloalkyl, optionally substituted heterocyclyl, optionally substituted aryl, or optionally substituted heteroaryl;

Y is a group selected from:



wherein,

R^{15} is selected from hydrogen, halogen, -CN, optionally substituted alkyl, optionally substituted fluoroalkyl, optionally substituted alkoxy, optionally substituted cycloalkyl, optionally substituted heterocyclyl, optionally substituted cycloalkylalkyl, optionally substituted cycloalkyl-O-, optionally substituted aryl, optionally substituted aralkyl, optionally substituted aryloxy, optionally substituted aralkyloxy, optionally substituted heteroaryloxy, optionally substituted heteroaralkyloxy, $-OR^{22}$, $-N(R^{22})_2$, $-SO_2R^{21}$, $-N(R^{22})SO_2R^{21}$, $-SO_2N(R^{22})_2$, $-N(R^{22})SO_2N(R^{22})_2$, $-CON(R^{22})_2$, $-N(R^{22})CO_2R^{21}$, $-N(R^{22})CON(R^{22})_2$, $-N(R^{22})COR^{21}$, $-OC(O)N(R^{22})_2$, $-OSO_2N(R^{22})_2$, or $-N(R^{22})SO_3R^{21}$;

R^{16} is selected from hydrogen, halogen, -CN, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted fluoroalkyl, optionally substituted alkoxy, optionally substituted cycloalkyl, optionally substituted heterocyclyl, optionally substituted cycloalkylalkyl, optionally substituted cycloalkyl-O-, optionally substituted aryl,

optionally substituted aralkyl, optionally substituted heteroaryl, optionally substituted heteroaralkyl, optionally substituted aryloxy, optionally substituted aralkyloxy, optionally substituted heteroaryloxy, optionally substituted heteroaralkyloxy, $-OR^{22}$, $-N(R^{22})_2$, $-SO_2R^{21}$, $-N(R^{22})SO_2R^{21}$, $-SO_2N(R^{22})_2$, $-N(R^{22})SO_2N(R^{22})_2$, $-CON(R^{22})_2$, $-N(R^{22})CO_2R^{21}$, $-N(R^{22})CON(R^{22})_2$, $-N(R^{22})COR^{21}$, $-OC(O)N(R^{22})_2$, $-OSO_2N(R^{22})_2$, or $-N(R^{22})SO_3R^{21}$;

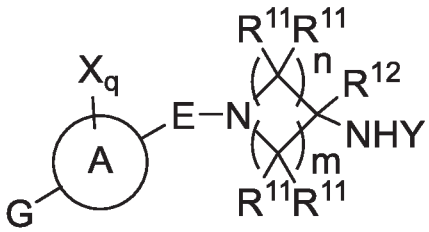
R^{17} is selected from hydrogen, halogen, -CN, optionally substituted alkyl, optionally substituted fluoroalkyl, optionally substituted alkoxy, optionally substituted cycloalkyl, optionally substituted heterocyclyl, optionally substituted cycloalkylalkyl, optionally substituted cycloalkyl-O-, optionally substituted aryl, optionally substituted aralkyl, optionally substituted aryloxy, optionally substituted aralkyloxy, optionally substituted heteroaryloxy, optionally substituted heteroaralkyloxy, $-OR^{22}$, $-N(R^{22})_2$, $-SO_2R^{21}$, $-N(R^{22})SO_2R^{21}$, $-SO_2N(R^{22})_2$, $-N(R^{22})SO_2N(R^{22})_2$, $-CON(R^{22})_2$, $-N(R^{22})CO_2R^{21}$, $-N(R^{22})CON(R^{22})_2$, $-N(R^{22})COR^{21}$, $-OC(O)N(R^{22})_2$, $-OSO_2N(R^{22})_2$, or $-N(R^{22})SO_3R^{21}$;

R^{18} is selected from hydrogen, halogen, -CN, optionally substituted alkyl, optionally substituted fluoroalkyl, optionally substituted alkoxy, optionally substituted cycloalkyl, optionally substituted heterocyclyl, optionally substituted cycloalkylalkyl, optionally substituted cycloalkyl-O-, optionally substituted aryl, optionally substituted aralkyl, optionally substituted heteroaryl, optionally substituted heteroaralkyl, optionally substituted aryloxy, optionally substituted aralkyloxy, optionally substituted heteroaryloxy, optionally substituted heteroaralkyloxy, $-OR^{22}$, $-N(R^{22})_2$, $-SO_2R^{21}$, $-N(R^{22})SO_2R^{21}$, $-SO_2N(R^{22})_2$, $-N(R^{22})SO_2N(R^{22})_2$, $-CON(R^{22})_2$, $-N(R^{22})CO_2R^{21}$, $-N(R^{22})CON(R^{22})_2$, $-N(R^{22})COR^{21}$, $-OC(O)N(R^{22})_2$, $-OSO_2N(R^{22})_2$, or $-N(R^{22})SO_3R^{21}$;

each R^{21} is independently selected from alkyl, cycloalkyl, cycloalkylalkyl, aryl, aralkyl, heterocyclyl, heterocyclylalkyl, heteroaryl, or heteroarylalkyl; and

each R^{22} is independently selected from hydrogen, alkyl, cycloalkyl, cycloalkylalkyl, aryl, aralkyl, heterocyclyl, heterocyclylalkyl, heteroaryl, or heteroarylalkyl.

[0005] One embodiment provides a compound, or pharmaceutically acceptable salt or solvate thereof, having the structure of Formula (II):



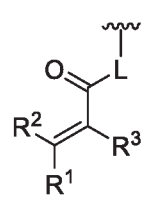
(II)

wherein,

ring A is a monocyclic heteroaryl;

E is selected from a bond, $-SO_2-$, $-C(O)-$, $-CH_2-$, $-CH(R^4)-$, or $-C(R^4)_2-$;

G is selected from a group having the structure: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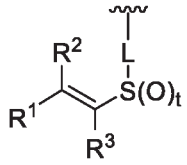
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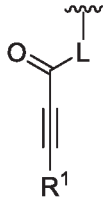
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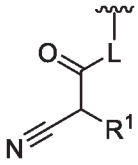
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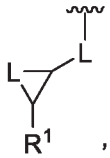
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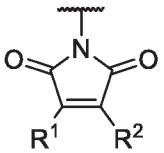
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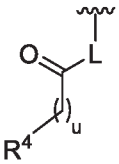
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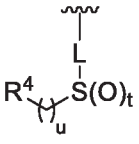
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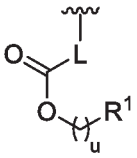
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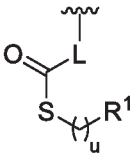
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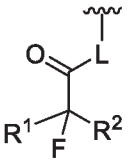
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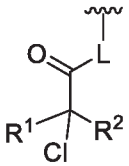
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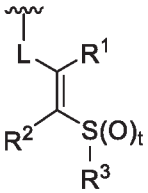
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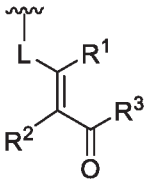
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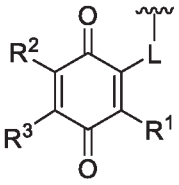
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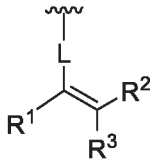
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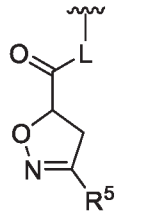
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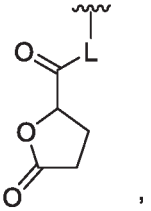
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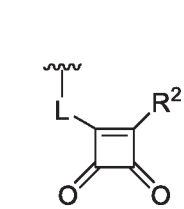
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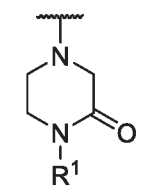
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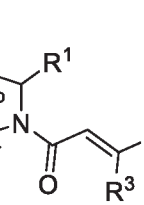
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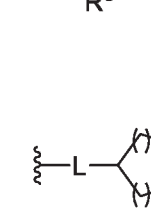
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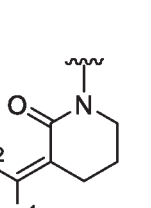
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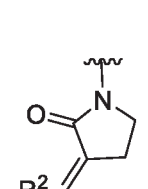
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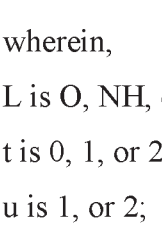
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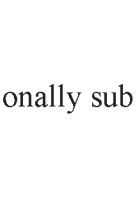
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wherein,

L is O, NH, or N(optionally substituted C1-C4 alkyl);

t is 0, 1, or 2;

u is 1, or 2;

p is 0, 1, or 2;

r is 0, 1, or 2;

R^1 is selected from hydrogen, optionally substituted C1-C4 alkyl, or optionally substituted heterocyclylalkyl;

R^2 is selected from hydrogen, or optionally substituted C1-C4 alkyl;

R^3 is selected from hydrogen, -CN, or optionally substituted C1-C4 alkyl;

each R^4 is independently selected from optionally substituted C1-C4 alkyl, or optionally substituted heterocyclylalkyl;

R^5 is optionally substituted C1-C4 alkyl, or optionally substituted heterocyclylalkyl;

each R^{11} is independently hydrogen, halogen, optionally substituted C1-C6 alkyl, -OH, optionally substituted C1-C4 alkoxy, or two R^{11} groups on the same carbon atom form an oxo;

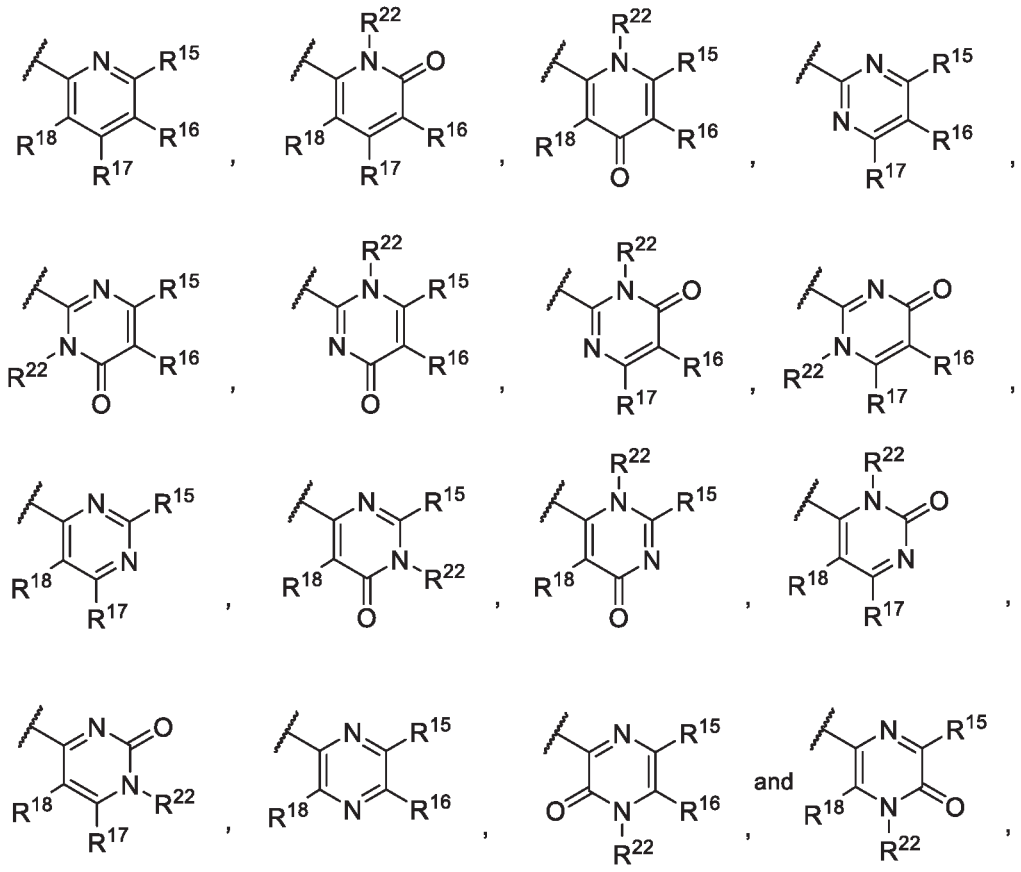
R^{12} is hydrogen or optionally substituted C1-C4 alkyl;

q is 0, 1, 2, or 3;

n is 0, 1, 2, or 3; m is 0, 1, 2, or 3;

each X is independently halogen, optionally substituted C1-C4 alkyl, optionally substituted C1-C4 alkoxy, optionally substituted aminoalkyl, optionally substituted cycloalkyl, optionally substituted heterocyclyl, optionally substituted aryl, or optionally substituted heteroaryl;

Y is a group selected from:



wherein,

R^{15} is selected from hydrogen, halogen, -CN, optionally substituted alkyl, optionally substituted fluoroalkyl, optionally substituted alkoxy, optionally substituted cycloalkyl, optionally substituted heterocyclyl, optionally substituted cycloalkylalkyl, optionally substituted cycloalkyl-O-, optionally substituted aryl, optionally substituted aralkyl, optionally substituted heteroaryl, optionally substituted heteroaralkyl, optionally substituted aryloxy, optionally substituted aralkyloxy, optionally substituted heteroaryloxy, optionally substituted heteroaralkyloxy, $-OR^{22}$, $-N(R^{22})_2$, $-SO_2R^{21}$, $-N(R^{22})SO_2R^{21}$, $-SO_2N(R^{22})_2$, $-N(R^{22})SO_2N(R^{22})_2$, $-CON(R^{22})_2$, $-N(R^{22})CO_2R^{21}$, $-N(R^{22})CON(R^{22})_2$, $-N(R^{22})COR^{21}$, $-OC(O)N(R^{22})_2$, $-OSO_2N(R^{22})_2$, or $-N(R^{22})SO_3R^{21}$;

R^{16} is selected from hydrogen, halogen, -CN, optionally substituted alkyl, optionally substituted fluoroalkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted alkoxy, optionally substituted cycloalkyl, optionally substituted heterocyclyl, optionally substituted cycloalkylalkyl, optionally substituted cycloalkyl-O-, optionally substituted aryl, optionally substituted aralkyl, optionally substituted heteroaryl, optionally substituted heteroaralkyl, optionally substituted aryloxy, optionally substituted aralkyloxy, optionally substituted heteroaryloxy, optionally substituted heteroaralkyloxy, $-OR^{22}$, $-N(R^{22})_2$, $-SO_2R^{21}$, $-N(R^{22})SO_2R^{21}$, $-SO_2N(R^{22})_2$, $-N(R^{22})SO_2N(R^{22})_2$, $-CON(R^{22})_2$, $-N(R^{22})CO_2R^{21}$, $-N(R^{22})CON(R^{22})_2$, $-N(R^{22})COR^{21}$, $-OC(O)N(R^{22})_2$, $-OSO_2N(R^{22})_2$, or $-N(R^{22})SO_3R^{21}$;

R^{17} is selected from hydrogen, halogen, -CN, optionally substituted alkyl, optionally substituted fluoroalkyl, optionally substituted alkoxy, optionally substituted cycloalkyl, optionally substituted heterocyclyl, optionally substituted cycloalkylalkyl, optionally substituted cycloalkyl-O-, optionally substituted aryl, optionally substituted aralkyl, optionally substituted heteroaryl, optionally substituted heteroaralkyl, optionally substituted aryloxy, optionally substituted aralkyloxy, optionally substituted heteroaryloxy, optionally substituted heteroaralkyloxy, $-OR^{22}$, $-N(R^{22})_2$, $-SO_2R^{21}$, $-N(R^{22})SO_2R^{21}$, $-SO_2N(R^{22})_2$, $-N(R^{22})SO_2N(R^{22})_2$, $-CON(R^{22})_2$, $-N(R^{22})CO_2R^{21}$, $-N(R^{22})CON(R^{22})_2$, $-N(R^{22})COR^{21}$, $-OC(O)N(R^{22})_2$, $-OSO_2N(R^{22})_2$, or $-N(R^{22})SO_3R^{21}$;

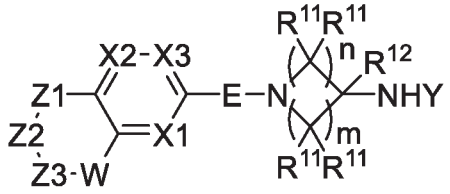
R^{18} is selected from hydrogen, halogen, -CN, optionally substituted alkyl, optionally substituted fluoroalkyl, optionally substituted alkoxy, optionally substituted cycloalkyl, optionally substituted heterocyclyl, optionally substituted cycloalkylalkyl, optionally substituted cycloalkyl-O-, optionally substituted aryl, optionally substituted aralkyl, optionally substituted heteroaryl, optionally substituted heteroaralkyl, optionally substituted aryloxy, optionally substituted aralkyloxy, optionally substituted heteroaryloxy, optionally substituted heteroaralkyloxy, $-OR^{22}$, $-N(R^{22})_2$, $-SO_2R^{21}$, $-N(R^{22})SO_2R^{21}$, $-SO_2N(R^{22})_2$, $-N(R^{22})SO_2N(R^{22})_2$,

$-CON(R^{22})_2$, $-N(R^{22})CO_2R^{21}$, $-N(R^{22})CON(R^{22})_2$, $-N(R^{22})COR^{21}$, $-OC(O)N(R^{22})_2$, $-OSO_2N(R^{22})_2$, or $-N(R^{22})SO_3R^{21}$;

each R^{21} is independently selected from alkyl, cycloalkyl, cycloalkylalkyl, aryl, aralkyl, heterocyclyl, heterocyclylalkyl, heteroaryl, or heteroarylalkyl; and

each R^{22} is independently selected from hydrogen, alkyl, cycloalkyl, cycloalkylalkyl, aryl, aralkyl, heterocyclyl, heterocyclylalkyl, heteroaryl, or heteroarylalkyl.

[0006] One embodiment provides a compound, or pharmaceutically acceptable salt or solvate thereof, having the structure of Formula (III):



(III)

wherein,

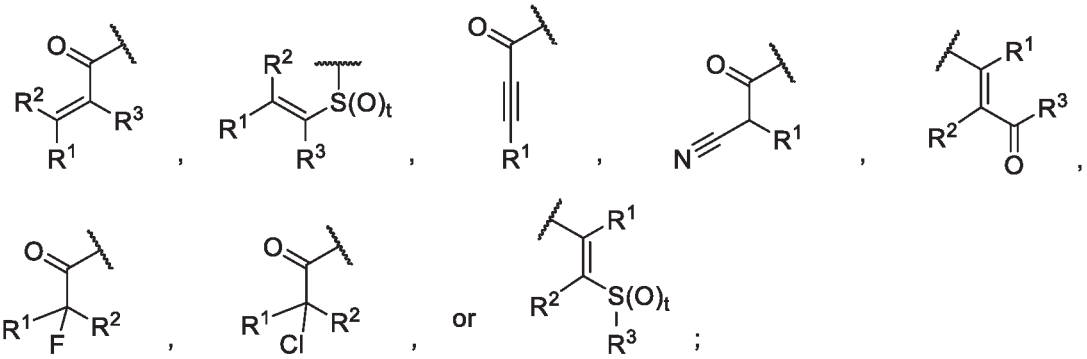
Z1, Z2, and Z3 are selected from CH_2 or N-G, with the provision that only one of Z1, Z2, or Z3 is N-G;

X1, X2 and X3 are each independently N or C-R^7;

W is absent, O, S, SO_2, NH, NR^{12}, $C(R^{11})_2$;

E is selected from a bond, $-SO_2-$, -C(O)-, $–CH_2-$, $-CH(R^4)-$, or $-C(R^4)_2-$;

G is selected from a group having the structure:



wherein,

t is 0, 1, or 2;

R^1 is selected from hydrogen, optionally substituted C1-C4 alkyl, or optionally substituted heterocyclylalkyl;

R^2 is selected from hydrogen, or optionally substituted C1-C4 alkyl;

R^3 is selected from hydrogen, -CN, or optionally substituted C1-C4 alkyl;

each R^4 is independently selected from optionally substituted C1-C4 alkyl, or optionally substituted heterocyclylalkyl;

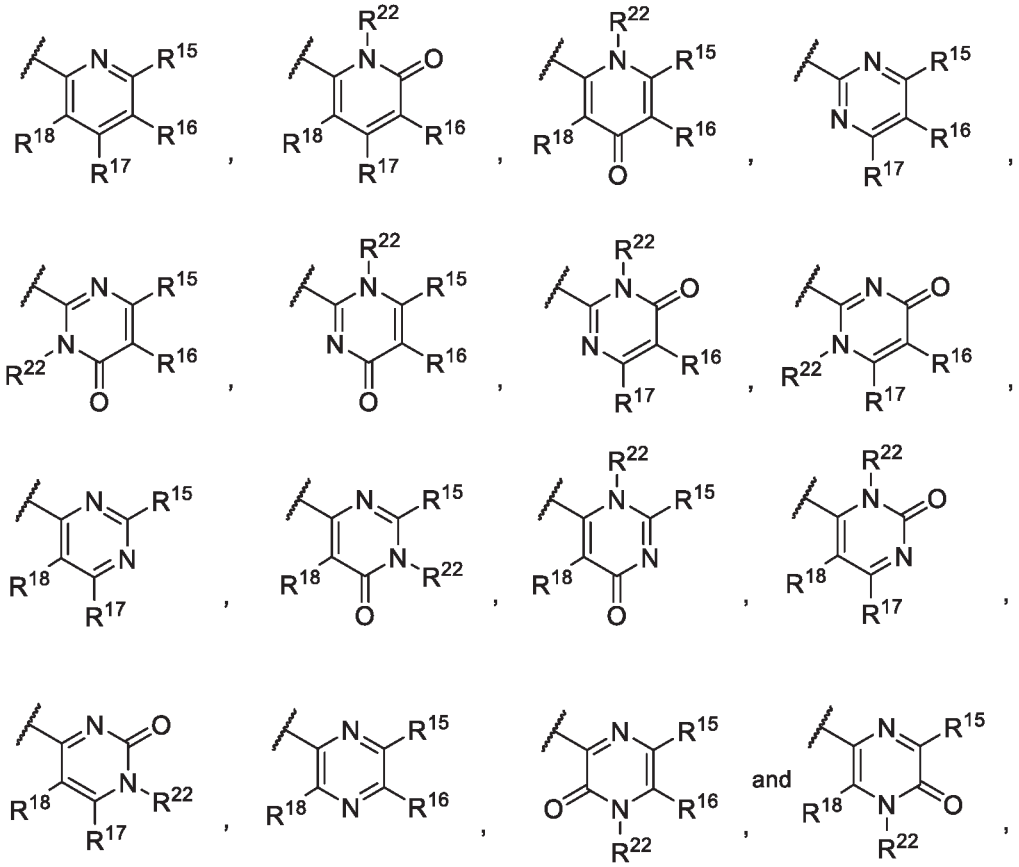
each R^7 is independently hydrogen, halogen, optionally substituted C1-C4 alkyl, optionally substituted C1-C4 alkoxy, optionally substituted cycloalkyl, optionally substituted heterocyclyl, optionally substituted aryl, or optionally substituted heteroaryl

each R^{11} is independently hydrogen, halogen, optionally substituted C1-C6 alkyl, or two R^{11} groups on the same carbon atom form an oxo;

each R^{12} is independently hydrogen or optionally substituted C1-C4 alkyl;

n is 0, 1, 2, or 3; m is 0, 1, 2, or 3;

Y is a group selected from:



wherein,

R^{15} is selected from hydrogen, halogen, -CN, optionally substituted alkyl, optionally substituted alkoxy, optionally substituted cycloalkyl, optionally substituted heterocyclyl, optionally substituted cycloalkylalkyl, optionally substituted cycloalkyl-O-, optionally substituted aryl, optionally substituted aralkyl, optionally substituted heteroaryl, optionally substituted heteroaralkyl, optionally substituted aryloxy, optionally substituted aralkyloxy, optionally substituted heteroaryloxy, optionally substituted heteroaralkyloxy, $-N(R^{22})_2$, $-SO_2R^{21}$, $-N(R^{22})SO_2R^{21}$, $-SO_2N(R^{22})_2$, $-N(R^{22})SO_2N(R^{22})_2$, $-CON(R^{22})_2$, $-N(R^{22})CO_2R^{21}$, $-N(R^{22})CON(R^{22})_2$, $-N(R^{22})COR^{21}$, $-OC(O)N(R^{22})_2$, $-OSO_2N(R^{22})_2$, or $-N(R^{22})SO_3R^{21}$;

R^{16} is selected from hydrogen, halogen, -CN, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted alkoxy, optionally substituted cycloalkyl, optionally substituted heterocyclyl, optionally substituted cycloalkylalkyl, optionally substituted cycloalkyl-O-, optionally substituted aryl, optionally substituted aralkyl, optionally substituted heteroaryl, optionally substituted heteroaralkyl, optionally substituted aryloxy, optionally substituted aralkyloxy, optionally substituted heteroaryloxy, optionally substituted heteroaralkyloxy, $-N(R^{22})_2$, $-SO_2R^{21}$, $-N(R^{22})SO_2R^{21}$, $-SO_2N(R^{22})_2$, $-N(R^{22})SO_2N(R^{22})_2$, $-CON(R^{22})_2$, $-N(R^{22})CO_2R^{21}$, $-N(R^{22})CON(R^{22})_2$, $-N(R^{22})COR^{21}$, $-OC(O)N(R^{22})_2$, $-OSO_2N(R^{22})_2$, or $-N(R^{22})SO_3R^{21}$;

R^{17} is selected from hydrogen, halogen, -CN, optionally substituted alkyl, optionally substituted alkoxy, optionally substituted cycloalkyl, optionally substituted heterocyclyl, optionally substituted cycloalkylalkyl, optionally substituted cycloalkyl-O-, optionally substituted aryl, optionally substituted aralkyl, optionally substituted heteroaryl, optionally substituted heteroaralkyl, optionally substituted aryloxy, optionally substituted aralkyloxy, optionally substituted heteroaryloxy, optionally substituted heteroaralkyloxy, $-N(R^{22})_2$, $-SO_2R^{21}$, $-N(R^{22})SO_2R^{21}$, $-SO_2N(R^{22})_2$, $-N(R^{22})SO_2N(R^{22})_2$, $-CON(R^{22})_2$, $-N(R^{22})CO_2R^{21}$, $-N(R^{22})CON(R^{22})_2$, $-N(R^{22})COR^{21}$, $-OC(O)N(R^{22})_2$, $-OSO_2N(R^{22})_2$, or $-N(R^{22})SO_3R^{21}$;

R^{18} is selected from hydrogen, halogen, -CN, optionally substituted alkyl, optionally substituted alkoxy, optionally substituted cycloalkyl, optionally substituted heterocyclyl, optionally substituted cycloalkylalkyl, optionally substituted cycloalkyl-O-, optionally substituted aryl, optionally substituted aralkyl, optionally substituted heteroaryl, optionally substituted heteroaralkyl, optionally substituted aryloxy, optionally substituted aralkyloxy, optionally substituted heteroaryloxy, optionally substituted heteroaralkyloxy, $-N(R^{22})_2$, $-SO_2R^{21}$, $-N(R^{22})SO_2R^{21}$, $-SO_2N(R^{22})_2$, $-N(R^{22})SO_2N(R^{22})_2$, $-CON(R^{22})_2$, $-N(R^{22})CO_2R^{21}$, $-N(R^{22})CON(R^{22})_2$, $-N(R^{22})COR^{21}$, $-OC(O)N(R^{22})_2$, $-OSO_2N(R^{22})_2$, or $-N(R^{22})SO_3R^{21}$;

each R^{21} is independently selected from alkyl, cycloalkyl, cycloalkylalkyl, aryl, aralkyl, heterocyclyl, heterocyclylalkyl, heteroaryl, or heteroarylalkyl; and

each R^{22} is independently selected from hydrogen, alkyl, cycloalkyl, cycloalkylalkyl, aryl, aralkyl, heterocyclyl, heterocyclylalkyl, heteroaryl, or heteroarylalkyl.

[0007] One embodiment provides a pharmaceutical composition comprising a compound of Formula (I), or pharmaceutically acceptable salt or solvate thereof, and at least one pharmaceutically acceptable excipient.

[0008] One embodiment provides a method of treating a disease or disorder in a patient in need thereof comprising administering to the patient a compound of Formula (I), or pharmaceutically acceptable

salt or solvate thereof. Another embodiment provides the method wherein the disease or disorder is cancer.

[0009] One embodiment provides a method of treating cancer in a patient in need thereof comprising administering to the patient a compound of Formula (I), or pharmaceutically acceptable salt or solvate thereof. Another embodiment provides the method wherein the disease or disorder is cancer.

[0010] One embodiment provides a pharmaceutical composition comprising a compound of Formula (II), or pharmaceutically acceptable salt or solvate thereof, and at least one pharmaceutically acceptable excipient.

[0011] One embodiment provides a method of treating a disease or disorder in a patient in need thereof comprising administering to the patient a compound of Formula (II), or pharmaceutically acceptable salt or solvate thereof. Another embodiment provides the method wherein the disease or disorder is cancer.

[0012] One embodiment provides a method of treating cancer in a patient in need thereof comprising administering to the patient a compound of Formula (II), or pharmaceutically acceptable salt or solvate thereof. Another embodiment provides the method wherein the disease or disorder is cancer.

[0013] One embodiment provides a pharmaceutical composition comprising a compound of Formula (III), or pharmaceutically acceptable salt or solvate thereof, and at least one pharmaceutically acceptable excipient.

[0014] One embodiment provides a method of treating a disease or disorder in a patient in need thereof comprising administering to the patient a compound of Formula (III), or pharmaceutically acceptable salt or solvate thereof. Another embodiment provides the method wherein the disease or disorder is cancer.

[0015] One embodiment provides a method of treating cancer in a patient in need thereof comprising administering to the patient a compound of Formula (III), or pharmaceutically acceptable salt or solvate thereof. Another embodiment provides the method wherein the disease or disorder is cancer.

INCORPORATION BY REFERENCE

[0016] All publications, patents, and patent applications mentioned in this specification are herein incorporated by reference for the specific purposes identified herein.

DETAILED DESCRIPTION OF THE INVENTION

[0017] As used herein and in the appended claims, the singular forms "a," "and," and "the" include plural referents unless the context clearly dictates otherwise. Thus, for example, reference to "an agent" includes a plurality of such agents, and reference to "the cell" includes reference to one or more cells (or to a plurality of cells) and equivalents thereof known to those skilled in the art, and so forth. When ranges are used herein for physical properties, such as molecular weight, or chemical properties, such as chemical formulae, all combinations and subcombinations of ranges and specific embodiments therein are intended to be included. The term "about" when referring to a number or a numerical range means that the number or numerical range referred to is an approximation within experimental variability (or within statistical experimental error), and thus the number or numerical range, in some instances, will vary between 1% and 15% of the stated number or numerical range. The term "comprising" (and related terms such as "comprise" or "comprises" or "having" or "including") is not intended to exclude that in other certain embodiments, for example, an embodiment of any composition of matter, composition, method, or process, or the like, described herein, "consist of" or "consist essentially of" the described features.

Definitions

[0018] As used in the specification and appended claims, unless specified to the contrary, the following terms have the meaning indicated below.

[0019] "Amino" refers to the $–NH_2$ radical.

[0020] "Cyano" refers to the -CN radical.

[0021] "Nitro" refers to the $-NO_2$ radical.

[0022] "Oxa" refers to the -O- radical.

[0023] "Oxo" refers to the =O radical.

[0024] "Thioxo" refers to the =S radical.

[0025] "Imino" refers to the =N-H radical.

[0026] "Oximo" refers to the =N-OH radical.

[0027] "Hydrazino" refers to the $=N-NH_2$ radical.

[0028] "Alkyl" refers to a straight or branched hydrocarbon chain radical consisting solely of carbon and hydrogen atoms, containing no unsaturation, having from one to fifteen carbon atoms (*e.g.*, C_1-C_{15} alkyl). In certain embodiments, an alkyl comprises one to thirteen carbon atoms (*e.g.*, C_1-C_{13} alkyl). In certain embodiments, an alkyl comprises one to eight carbon atoms (*e.g.*, C_1-C_8 alkyl). In other embodiments, an alkyl comprises one to five carbon atoms (*e.g.*, C_1-C_5 alkyl). In other embodiments, an alkyl comprises one to four carbon atoms (*e.g.*, C_1-C_4 alkyl). In other embodiments, an alkyl comprises one to three carbon atoms (*e.g.*, C_1-C_3 alkyl). In other

embodiments, an alkyl comprises one to two carbon atoms (*e.g.*, C_1-C_2 alkyl). In other embodiments, an alkyl comprises one carbon atom (*e.g.*, C_1 alkyl). In other embodiments, an alkyl comprises five to fifteen carbon atoms (*e.g.*, C_5-C_{15} alkyl). In other embodiments, an alkyl comprises five to eight carbon atoms (*e.g.*, C_5-C_8 alkyl). In other embodiments, an alkyl comprises two to five carbon atoms (*e.g.*, C_2-C_5 alkyl). In other embodiments, an alkyl comprises three to five carbon atoms (*e.g.*, C_3-C_5 alkyl). In other embodiments, the alkyl group is selected from methyl, ethyl, 1-propyl (*n*-propyl), 1-methylethyl (*iso*-propyl), 1-butyl (*n*-butyl), 1-methylpropyl (*sec*-butyl), 2-methylpropyl (*iso*-butyl), 1,1-dimethylethyl (*tert*-butyl), 1-pentyl (*n*-pentyl). The alkyl is attached to the rest of the molecule by a single bond. Unless stated otherwise specifically in the specification, an alkyl group is optionally substituted by one or more of the following substituents: halo, cyano, nitro, oxo, thioxo, imino, oximo, trimethylsilanyl, $-OR^a$, $-SR^a$, $-OC(O)-R^a$, $-N(R^a)_2$, $-C(O)R^a$, $-C(O)OR^a$, $-C(O)N(R^a)_2$, $-N(R^a)C(O)OR^a$, $-OC(O)-N(R^a)_2$, $-N(R^a)C(O)R^a$, $-N(R^a)S(O)_tR^a$ (where t is 1 or 2), $-S(O)_tOR^a$ (where t is 1 or 2), $-S(O)_tR^a$ (where t is 1 or 2) and $-S(O)_tN(R^a)_2$ (where t is 1 or 2) where each R^a is independently hydrogen, alkyl (optionally substituted with halogen, hydroxy, methoxy, or trifluoromethyl), fluoroalkyl, carbocyclyl (optionally substituted with halogen, hydroxy, methoxy, or trifluoromethyl), carbocyclylalkyl (optionally substituted with halogen, hydroxy, methoxy, or trifluoromethyl), aryl (optionally substituted with halogen, hydroxy, methoxy, or trifluoromethyl), aralkyl (optionally substituted with halogen, hydroxy, methoxy, or trifluoromethyl), heterocyclyl (optionally substituted with halogen, hydroxy, methoxy, or trifluoromethyl), heterocyclylalkyl (optionally substituted with halogen, hydroxy, methoxy, or trifluoromethyl), heteroaryl (optionally substituted with halogen, hydroxy, methoxy, or trifluoromethyl), or heteroarylalkyl (optionally substituted with halogen, hydroxy, methoxy, or trifluoromethyl).

[0029] "Alkoxy" refers to a radical bonded through an oxygen atom of the formula –O-alkyl, where alkyl is an alkyl chain as defined above.

[0030] "Alkenyl" refers to a straight or branched hydrocarbon chain radical group consisting solely of carbon and hydrogen atoms, containing at least one carbon-carbon double bond, and having from two to twelve carbon atoms. In certain embodiments, an alkenyl comprises two to eight carbon atoms. In other embodiments, an alkenyl comprises two to four carbon atoms. The alkenyl is attached to the rest of the molecule by a single bond, for example, ethenyl (*i.e.*, vinyl), prop-1-enyl (*i.e.*, allyl), but-1-enyl, pent-1-enyl, penta-1,4-dienyl, and the like. Unless stated otherwise specifically in the specification, an alkenyl group is optionally substituted by one or more of the following substituents: halo, cyano, nitro, oxo, thioxo, imino, oximo, trimethylsilanyl, $-OR^a$, $-SR^a$, $-OC(O)-R^a$, $-N(R^a)_2$, $-C(O)R^a$, $-C(O)OR^a$, $-C(O)N(R^a)_2$, $-N(R^a)C(O)OR^a$, $-OC(O)-N(R^a)_2$, -

$N(R^a)C(O)R^a$, $-N(R^a)S(O)_tR^a$ (where t is 1 or 2), $-S(O)_tOR^a$ (where t is 1 or 2), $-S(O)_tR^a$ (where t is 1 or 2) and $-S(O)_tN(R^a)_2$ (where t is 1 or 2) where each R^a is independently hydrogen, alkyl (optionally substituted with halogen, hydroxy, methoxy, or trifluoromethyl), fluoroalkyl, carbocyclyl (optionally substituted with halogen, hydroxy, methoxy, or trifluoromethyl), carbocyclylalkyl (optionally substituted with halogen, hydroxy, methoxy, or trifluoromethyl), aryl (optionally substituted with halogen, hydroxy, methoxy, or trifluoromethyl), aralkyl (optionally substituted with halogen, hydroxy, methoxy, or trifluoromethyl), heterocyclyl (optionally substituted with halogen, hydroxy, methoxy, or trifluoromethyl), heterocyclylalkyl (optionally substituted with halogen, hydroxy, methoxy, or trifluoromethyl), heteroaryl (optionally substituted with halogen, hydroxy, methoxy, or trifluoromethyl), or heteroarylalkyl (optionally substituted with halogen, hydroxy, methoxy, or trifluoromethyl).

[0031] "Alkynyl" refers to a straight or branched hydrocarbon chain radical group consisting solely of carbon and hydrogen atoms, containing at least one carbon-carbon triple bond, having from two to twelve carbon atoms. In certain embodiments, an alkynyl comprises two to eight carbon atoms. In other embodiments, an alkynyl comprises two to six carbon atoms. In other embodiments, an alkynyl comprises two to four carbon atoms. The alkynyl is attached to the rest of the molecule by a single bond, for example, ethynyl, propynyl, butynyl, pentynyl, hexynyl, and the like. Unless stated otherwise specifically in the specification, an alkynyl group is optionally substituted by one or more of the following substituents: halo, cyano, nitro, oxo, thioxo, imino, oximo, trimethylsilanyl, $-OR^a$, $-SR^a$, $-OC(O)-R^a$, $-N(R^a)_2$, $-C(O)R^a$, $-C(O)OR^a$, $-C(O)N(R^a)_2$, $-N(R^a)C(O)OR^a$, $-OC(O)-N(R^a)_2$, $-N(R^a)C(O)R^a$, $-N(R^a)S(O)_tR^a$ (where t is 1 or 2), $-S(O)_tOR^a$ (where t is 1 or 2), $-S(O)_tR^a$ (where t is 1 or 2) and $-S(O)_tN(R^a)_2$ (where t is 1 or 2) where each R^a is independently hydrogen, alkyl (optionally substituted with halogen, hydroxy, methoxy, or trifluoromethyl), fluoroalkyl, carbocyclyl (optionally substituted with halogen, hydroxy, methoxy, or trifluoromethyl), carbocyclylalkyl (optionally substituted with halogen, hydroxy, methoxy, or trifluoromethyl), aryl (optionally substituted with halogen, hydroxy, methoxy, or trifluoromethyl), aralkyl (optionally substituted with halogen, hydroxy, methoxy, or trifluoromethyl), heterocyclyl (optionally substituted with halogen, hydroxy, methoxy, or trifluoromethyl), heterocyclylalkyl (optionally substituted with halogen, hydroxy, methoxy, or trifluoromethyl), heteroaryl (optionally substituted with halogen, hydroxy, methoxy, or trifluoromethyl), or heteroarylalkyl (optionally substituted with halogen, hydroxy, methoxy, or trifluoromethyl).

[0032] "Alkylene" or "alkylene chain" refers to a straight or branched divalent hydrocarbon chain linking the rest of the molecule to a radical group, consisting solely of carbon and hydrogen, containing no unsaturation and having from one to twelve carbon atoms, for example, methylene, ethylene,

propylene, *n*-butylene, and the like. The alkylene chain is attached to the rest of the molecule through a single bond and to the radical group through a single bond. The points of attachment of the alkylene chain to the rest of the molecule and to the radical group are through one carbon in the alkylene chain or through any two carbons within the chain. In certain embodiments, an alkylene comprises one to eight carbon atoms (*e.g.*, C_1-C_8 alkylene). In other embodiments, an alkylene comprises one to five carbon atoms (*e.g.*, C_1-C_5 alkylene). In other embodiments, an alkylene comprises one to four carbon atoms (*e.g.*, C_1-C_4 alkylene). In other embodiments, an alkylene comprises one to three carbon atoms (*e.g.*, C_1-C_3 alkylene). In other embodiments, an alkylene comprises one to two carbon atoms (*e.g.*, C_1-C_2 alkylene). In other embodiments, an alkylene comprises one carbon atom (*e.g.*, C_1 alkylene). In other embodiments, an alkylene comprises five to eight carbon atoms (*e.g.*, C_5-C_8 alkylene). In other embodiments, an alkylene comprises two to five carbon atoms (*e.g.*, C_2-C_5 alkylene). In other embodiments, an alkylene comprises three to five carbon atoms (*e.g.*, C_3-C_5 alkylene). Unless stated otherwise specifically in the specification, an alkylene chain is optionally substituted by one or more of the following substituents: halo, cyano, nitro, oxo, thioxo, imino, oximo, trimethylsilanyl, $-OR^a$, $-SR^a$, $-OC(O)-R^a$, $-N(R^a)_2$, $-C(O)R^a$, $-C(O)OR^a$, $-C(O)N(R^a)_2$, $-N(R^a)C(O)OR^a$, $-OC(O)-N(R^a)_2$, $-N(R^a)C(O)R^a$, $-N(R^a)S(O)_tR^a$ (where t is 1 or 2), $-S(O)_tOR^a$ (where t is 1 or 2), $-S(O)_tR^a$ (where t is 1 or 2) and $-S(O)_tN(R^a)_2$ (where t is 1 or 2) where each R^a is independently hydrogen, alkyl (optionally substituted with halogen, hydroxy, methoxy, or trifluoromethyl), fluoroalkyl, carbocyclyl (optionally substituted with halogen, hydroxy, methoxy, or trifluoromethyl), carbocyclylalkyl (optionally substituted with halogen, hydroxy, methoxy, or trifluoromethyl), aryl (optionally substituted with halogen, hydroxy, methoxy, or trifluoromethyl), aralkyl (optionally substituted with halogen, hydroxy, methoxy, or trifluoromethyl), heterocyclyl (optionally substituted with halogen, hydroxy, methoxy, or trifluoromethyl), heterocyclylalkyl (optionally substituted with halogen, hydroxy, methoxy, or trifluoromethyl), heteroaryl (optionally substituted with halogen, hydroxy, methoxy, or trifluoromethyl), or heteroarylalkyl (optionally substituted with halogen, hydroxy, methoxy, or trifluoromethyl).

[0033] "Alkenylene" or "alkenylene chain" refers to a straight or branched divalent hydrocarbon chain linking the rest of the molecule to a radical group, consisting solely of carbon and hydrogen, containing at least one carbon-carbon double bond, and having from two to twelve carbon atoms. The alkenylene chain is attached to the rest of the molecule through a single bond and to the radical group through a single bond. In certain embodiments, an alkenylene comprises two to eight carbon atoms (*e.g.*, C_2-C_8 alkenylene). In other embodiments, an alkenylene comprises two to five carbon atoms (*e.g.*, C_2-C_5 alkenylene). In other embodiments, an alkenylene comprises two to four carbon

atoms (*e.g.*, C_2-C_4 alkenylene). In other embodiments, an alkenylene comprises two to three carbon atoms (*e.g.*, C_2-C_3 alkenylene). In other embodiments, an alkenylene comprises two carbon atoms (*e.g.*, C_2 alkenylene). In other embodiments, an alkenylene comprises five to eight carbon atoms (*e.g.*, C_5-C_8 alkenylene). In other embodiments, an alkenylene comprises three to five carbon atoms (*e.g.*, C_3-C_5 alkenylene). Unless stated otherwise specifically in the specification, an alkenylene chain is optionally substituted by one or more of the following substituents: halo, cyano, nitro, oxo, thioxo, imino, oximo, trimethylsilanyl, $-OR^a$, $-SR^a$, $-OC(O)-R^a$, $-N(R^a)_2$, $-C(O)R^a$, $-C(O)OR^a$, $-C(O)N(R^a)_2$, $-N(R^a)C(O)OR^a$, $-OC(O)-N(R^a)_2$, $-N(R^a)C(O)R^a$, $-N(R^a)S(O)_tR^a$ (where t is 1 or 2), $-S(O)_tOR^a$ (where t is 1 or 2), $-S(O)_tR^a$ (where t is 1 or 2) and $-S(O)_tN(R^a)_2$ (where t is 1 or 2) where each R^a is independently hydrogen, alkyl (optionally substituted with halogen, hydroxy, methoxy, or trifluoromethyl), fluoroalkyl, carbocyclyl (optionally substituted with halogen, hydroxy, methoxy, or trifluoromethyl), carbocyclylalkyl (optionally substituted with halogen, hydroxy, methoxy, or trifluoromethyl), aryl (optionally substituted with halogen, hydroxy, methoxy, or trifluoromethyl), aralkyl (optionally substituted with halogen, hydroxy, methoxy, or trifluoromethyl), heterocyclyl (optionally substituted with halogen, hydroxy, methoxy, or trifluoromethyl), heterocyclylalkyl (optionally substituted with halogen, hydroxy, methoxy, or trifluoromethyl), heteroaryl (optionally substituted with halogen, hydroxy, methoxy, or trifluoromethyl), or heteroarylalkyl (optionally substituted with halogen, hydroxy, methoxy, or trifluoromethyl).

[0034] "Alkynylene" or "alkynylene chain" refers to a straight or branched divalent hydrocarbon chain linking the rest of the molecule to a radical group, consisting solely of carbon and hydrogen, containing at least one carbon-carbon triple bond, and having from two to twelve carbon atoms. The alkynylene chain is attached to the rest of the molecule through a single bond and to the radical group through a single bond. In certain embodiments, an alkynylene comprises two to eight carbon atoms (*e.g.*, C_2-C_8 alkynylene). In other embodiments, an alkynylene comprises two to five carbon atoms (*e.g.*, C_2-C_5 alkynylene). In other embodiments, an alkynylene comprises two to four carbon atoms (*e.g.*, C_2-C_4 alkynylene). In other embodiments, an alkynylene comprises two to three carbon atoms (*e.g.*, C_2-C_3 alkynylene). In other embodiments, an alkynylene comprises two carbon atoms (*e.g.*, C_2 alkynylene). In other embodiments, an alkynylene comprises five to eight carbon atoms (*e.g.*, C_5-C_8 alkynylene). In other embodiments, an alkynylene comprises three to five carbon atoms (*e.g.*, C_3-C_5 alkynylene). Unless stated otherwise specifically in the specification, an alkynylene chain is optionally substituted by one or more of the following substituents: halo, cyano, nitro, oxo, thioxo, imino, oximo, trimethylsilanyl, $-OR^a$, $-SR^a$, $-OC(O)-R^a$, $-N(R^a)_2$, $-C(O)R^a$, $-C(O)OR^a$, $-C(O)N(R^a)_2$, $-N(R^a)C(O)OR^a$, $-OC(O)-N(R^a)_2$, $-N(R^a)C(O)R^a$, $-N(R^a)S(O)_tR^a$ (where t is

1 or 2), $-S(O)_tOR^a$ (where t is 1 or 2), $-S(O)_tR^a$ (where t is 1 or 2) and $-S(O)_tN(R^a)_2$ (where t is 1 or 2) where each R^a is independently hydrogen, alkyl (optionally substituted with halogen, hydroxy, methoxy, or trifluoromethyl), fluoroalkyl, carbocyclyl (optionally substituted with halogen, hydroxy, methoxy, or trifluoromethyl), carbocyclylalkyl (optionally substituted with halogen, hydroxy, methoxy, or trifluoromethyl), aryl (optionally substituted with halogen, hydroxy, methoxy, or trifluoromethyl), aralkyl (optionally substituted with halogen, hydroxy, methoxy, or trifluoromethyl), heterocyclyl (optionally substituted with halogen, hydroxy, methoxy, or trifluoromethyl), heterocyclylalkyl (optionally substituted with halogen, hydroxy, methoxy, or trifluoromethyl), heteroaryl (optionally substituted with halogen, hydroxy, methoxy, or trifluoromethyl), or heteroarylalkyl (optionally substituted with halogen, hydroxy, methoxy, or trifluoromethyl).

[0035] "Amionoalkyl" refers to a $-N(alkyl)_2$ radical, wherein each “alkyl” is independently as defined above, for example, dimethylamino, ethyl(methyl)amino, 2-aminoethyl)(methyl)amino, (2-(dimethylamino)ethyl)(methyl)amino, and the like. In some embodiments, the alkyl part of the aminoalkyl radical is optionally substituted as defined above for an alkyl group.

[0036] "Aryl" refers to a radical derived from an aromatic monocyclic or multicyclic hydrocarbon ring system by removing a hydrogen atom from a ring carbon atom. The aromatic monocyclic or multicyclic hydrocarbon ring system contains only hydrogen and carbon from five to eighteen carbon atoms, where at least one of the rings in the ring system is fully unsaturated, *i.e.*, it contains a cyclic, delocalized (4n+2) π–electron system in accordance with the Hückel theory. The ring system from which aryl groups are derived include, but are not limited to, groups such as benzene, fluorene, indane, indene, tetralin and naphthalene. Unless stated otherwise specifically in the specification, the term "aryl" or the prefix "ar-" (such as in "aralkyl") is meant to include aryl radicals optionally substituted by one or more substituents independently selected from alkyl, alkenyl, alkynyl, halo, fluoroalkyl, cyano, nitro, optionally substituted aryl, optionally substituted aralkyl, optionally substituted aralkenyl, optionally substituted aralkynyl, optionally substituted carbocyclyl, optionally substituted carbocyclylalkyl, optionally substituted heterocyclyl, optionally substituted heterocyclylalkyl, optionally substituted heteroaryl, optionally substituted heteroarylalkyl, $-R^b-OR^a$, $-R^b-OC(O)-R^a$, $-R^b-OC(O)-OR^a$, $-R^b-OC(O)-N(R^a)_2$, $-R^b-N(R^a)_2$, $-R^b-C(O)R^a$, $-R^b-C(O)OR^a$, $-R^b-C(O)N(R^a)_2$, $-R^b-O-R^c-C(O)N(R^a)_2$, $-R^b-N(R^a)C(O)OR^a$, $-R^b-N(R^a)C(O)R^a$, $-R^b-N(R^a)S(O)_tR^a$ (where t is 1 or 2), $-R^b-S(O)_tR^a$ (where t is 1 or 2), $-R^b-S(O)_tOR^a$ (where t is 1 or 2) and $-R^b-S(O)_tN(R^a)_2$ (where t is 1 or 2), where each R^a is independently hydrogen, alkyl (optionally substituted with halogen, hydroxy, methoxy, or trifluoromethyl), fluoroalkyl, cycloalkyl (optionally substituted with halogen, hydroxy, methoxy, or trifluoromethyl),

cycloalkylalkyl (optionally substituted with halogen, hydroxy, methoxy, or trifluoromethyl), aryl (optionally substituted with halogen, hydroxy, methoxy, or trifluoromethyl), aralkyl (optionally substituted with halogen, hydroxy, methoxy, or trifluoromethyl), heterocyclyl (optionally substituted with halogen, hydroxy, methoxy, or trifluoromethyl), heterocyclylalkyl (optionally substituted with halogen, hydroxy, methoxy, or trifluoromethyl), heteroaryl (optionally substituted with halogen, hydroxy, methoxy, or trifluoromethyl), or heteroarylalkyl (optionally substituted with halogen, hydroxy, methoxy, or trifluoromethyl), each R^b is independently a direct bond or a straight or branched alkylene or alkenylene chain, and R^c is a straight or branched alkylene or alkenylene chain, and where each of the above substituents is unsubstituted unless otherwise indicated.

[0037] "Aralkyl" refers to a radical of the formula -R^c-aryl where R^c is an alkylene chain as defined above, for example, methylene, ethylene, and the like. The alkylene chain part of the aralkyl radical is optionally substituted as described above for an alkylene chain. The aryl part of the aralkyl radical is optionally substituted as described above for an aryl group.

[0038] "Aralkenyl" refers to a radical of the formula –R^d-aryl where R^d is an alkenylene chain as defined above. The aryl part of the aralkenyl radical is optionally substituted as described above for an aryl group. The alkenylene chain part of the aralkenyl radical is optionally substituted as defined above for an alkenylene group.

[0039] "Aralkynyl" refers to a radical of the formula -R^e-aryl, where R^e is an alkynylene chain as defined above. The aryl part of the aralkynyl radical is optionally substituted as described above for an aryl group. The alkynylene chain part of the aralkynyl radical is optionally substituted as defined above for an alkynylene chain.

[0040] "Aralkoxy" refers to a radical bonded through an oxygen atom of the formula -O-R^c-aryl where R^c is an alkylene chain as defined above, for example, methylene, ethylene, and the like. The alkylene chain part of the aralkyl radical is optionally substituted as described above for an alkylene chain. The aryl part of the aralkyl radical is optionally substituted as described above for an aryl group.

[0041] "Carbocyclyl" refers to a stable non-aromatic monocyclic or polycyclic hydrocarbon radical consisting solely of carbon and hydrogen atoms, which includes fused or bridged ring systems, having from three to fifteen carbon atoms. In certain embodiments, a carbocyclyl comprises three to ten carbon atoms. In other embodiments, a carbocyclyl comprises five to seven carbon atoms. The carbocyclyl is attached to the rest of the molecule by a single bond. Carbocyclyl is saturated (*i.e.*, containing single C-C bonds only) or unsaturated (*i.e.*, containing one or more double bonds or triple bonds). A fully saturated carbocyclyl radical is also referred to as "cycloalkyl." Examples of monocyclic cycloalkyls include, *e.g.*, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, and cyclooctyl. An unsaturated carbocyclyl is also referred to as "cycloalkenyl."

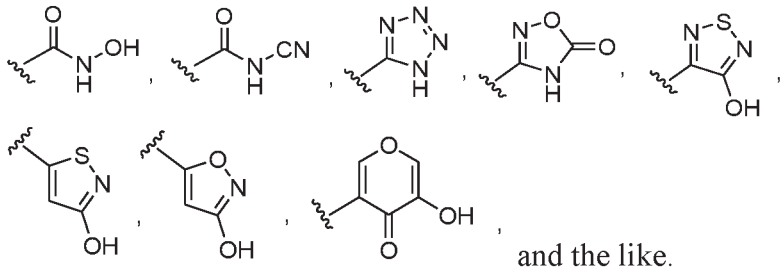
Examples of monocyclic cycloalkenyls include, *e.g.*, cyclopentenyl, cyclohexenyl, cycloheptenyl, and cyclooctenyl. Polycyclic carbocyclyl radicals include, for example, adamantyl, norbornyl (*i.e.*, bicyclo[2.2.1]heptanyl), norbornenyl, decalinyl, 7,7-dimethyl-bicyclo[2.2.1]heptanyl, and the like. Unless otherwise stated specifically in the specification, the term "carbocyclyl" is meant to include carbocyclyl radicals that are optionally substituted by one or more substituents independently selected from alkyl, alkenyl, alkynyl, halo, fluoroalkyl, oxo, thioxo, cyano, nitro, optionally substituted aryl, optionally substituted aralkyl, optionally substituted aralkenyl, optionally substituted aralkynyl, optionally substituted carbocyclyl, optionally substituted carbocyclylalkyl, optionally substituted heterocyclyl, optionally substituted heterocyclylalkyl, optionally substituted heteroaryl, optionally substituted heteroarylalkyl, $-R^b-OR^a$, $-R^b-OC(O)-R^a$, $-R^b-OC(O)-OR^a$, $-R^b-OC(O)-N(R^a)_2$, $-R^b-N(R^a)_2$, $-R^b-C(O)R^a$, $-R^b-C(O)OR^a$, $-R^b-C(O)N(R^a)_2$, $-R^b-O-R^c-C(O)N(R^a)_2$, $-R^b-N(R^a)C(O)OR^a$, $-R^b-N(R^a)C(O)R^a$, $-R^b-N(R^a)S(O)_tR^a$ (where t is 1 or 2), $-R^b-S(O)_tR^a$ (where t is 1 or 2), $-R^b-S(O)_tOR^a$ (where t is 1 or 2) and $-R^b-S(O)_tN(R^a)_2$ (where t is 1 or 2), where each R^a is independently hydrogen, alkyl (optionally substituted with halogen, hydroxy, methoxy, or trifluoromethyl), fluoroalkyl, cycloalkyl (optionally substituted with halogen, hydroxy, methoxy, or trifluoromethyl), cycloalkylalkyl (optionally substituted with halogen, hydroxy, methoxy, or trifluoromethyl), aryl (optionally substituted with halogen, hydroxy, methoxy, or trifluoromethyl), aralkyl (optionally substituted with halogen, hydroxy, methoxy, or trifluoromethyl), heterocyclyl (optionally substituted with halogen, hydroxy, methoxy, or trifluoromethyl), heterocyclylalkyl (optionally substituted with halogen, hydroxy, methoxy, or trifluoromethyl), heteroaryl (optionally substituted with halogen, hydroxy, methoxy, or trifluoromethyl), or heteroarylalkyl (optionally substituted with halogen, hydroxy, methoxy, or trifluoromethyl), each R^b is independently a direct bond or a straight or branched alkylene or alkenylene chain, and R^c is a straight or branched alkylene or alkenylene chain, and where each of the above substituents is unsubstituted unless otherwise indicated.

[0042] "Carbocyclylalkyl" refers to a radical of the formula $-R^c$-carbocyclyl where R^c is an alkylene chain as defined above. The alkylene chain and the carbocyclyl radical is optionally substituted as defined above.

[0043] "Carbocyclylalkynyl" refers to a radical of the formula $-R^c$-carbocyclyl where R^c is an alkynylene chain as defined above. The alkynylene chain and the carbocyclyl radical is optionally substituted as defined above.

[0044] "Carbocyclylalkoxy" refers to a radical bonded through an oxygen atom of the formula $-O-R^c$-carbocyclyl where R^c is an alkylene chain as defined above. The alkylene chain and the carbocyclyl radical is optionally substituted as defined above.

[0045] As used herein, "carboxylic acid bioisostere" refers to a functional group or moiety that exhibits similar physical, biological and/or chemical properties as a carboxylic acid moiety. Examples of carboxylic acid bioisosteres include, but are not limited to,



and the like.

[0046] "Halo" or "halogen" refers to bromo, chloro, fluoro or iodo substituents.

[0047] "Fluoroalkyl" refers to an alkyl radical, as defined above, that is substituted by one or more fluoro radicals, as defined above, for example, trifluoromethyl, difluoromethyl, fluoromethyl, 2,2,2-trifluoroethyl, 1-fluoromethyl-2-fluoroethyl, and the like. In some embodiments, the alkyl part of the fluoroalkyl radical is optionally substituted as defined above for an alkyl group.

[0048] "Heterocyclyl" refers to a stable 3- to 18-membered non-aromatic ring radical that comprises two to twelve carbon atoms and from one to six heteroatoms selected from nitrogen, oxygen and sulfur. Unless stated otherwise specifically in the specification, the heterocyclyl radical is a monocyclic, bicyclic, tricyclic or tetracyclic ring system, which optionally includes fused or bridged ring systems. The heteroatoms in the heterocyclyl radical are optionally oxidized. One or more nitrogen atoms, if present, are optionally quaternized. The heterocyclyl radical is partially or fully saturated. The heterocyclyl is attached to the rest of the molecule through any atom of the ring(s). Examples of such heterocyclyl radicals include, but are not limited to, dioxolanyl, thienyl[1,3]dithianyl, decahydroisoquinolyl, imidazolinyl, imidazolidinyl, isothiazolidinyl, isoxazolidinyl, morpholinyl, octahydroindolyl, octahydroisoindolyl, 2-oxopiperazinyl, 2-oxopiperidinyl, 2-oxopyrrolidinyl, oxazolidinyl, piperidinyl, piperazinyl, 4-piperidonyl, pyrrolidinyl, pyrazolidinyl, quinuclidinyl, thiazolidinyl, tetrahydrofuryl, trithianyl, tetrahydropyranyl, thiomorpholinyl, thiamorpholinyl, 1-oxo-thiomorpholinyl, and 1,1-dioxo-thiomorpholinyl. Unless stated otherwise specifically in the specification, the term "heterocyclyl" is meant to include heterocyclyl radicals as defined above that are optionally substituted by one or more substituents selected from alkyl, alkenyl, alkynyl, halo, fluoroalkyl, oxo, thioxo, cyano, nitro, optionally substituted aryl, optionally substituted aralkyl, optionally substituted aralkenyl, optionally substituted aralkynyl, optionally substituted carbocyclyl, optionally substituted carbocyclylalkyl, optionally substituted heterocyclyl, optionally substituted heterocyclylalkyl, optionally substituted heteroaryl, optionally substituted heteroarylalkyl, $-R^b-OR^a$, $-R^b-OC(O)-R^a$, $-R^b-OC(O)-OR^a$, $-R^b-OC(O)-N(R^a)_2$, $-R^b-N(R^a)_2$, $-R^b-C(O)R^a$, $-R^b-C(O)OR^a$, $-R^b-C(O)N(R^a)_2$, $-R^b-O-R^c-C(O)N(R^a)_2$, $-R^b-N(R^a)C(O)OR^a$, $-R^b-$

$N(R^a)C(O)R^a$, $-R^b-N(R^a)S(O)_tR^a$ (where t is 1 or 2), $-R^b-S(O)_tR^a$ (where t is 1 or 2), $-R^b-S(O)_tOR^a$ (where t is 1 or 2) and $-R^b-S(O)_tN(R^a)_2$ (where t is 1 or 2), where each R^a is independently hydrogen, alkyl (optionally substituted with halogen, hydroxy, methoxy, or trifluoromethyl), fluoroalkyl, cycloalkyl (optionally substituted with halogen, hydroxy, methoxy, or trifluoromethyl), cycloalkylalkyl (optionally substituted with halogen, hydroxy, methoxy, or trifluoromethyl), aryl (optionally substituted with halogen, hydroxy, methoxy, or trifluoromethyl), aralkyl (optionally substituted with halogen, hydroxy, methoxy, or trifluoromethyl), heterocyclyl (optionally substituted with halogen, hydroxy, methoxy, or trifluoromethyl), heterocyclylalkyl (optionally substituted with halogen, hydroxy, methoxy, or trifluoromethyl), heteroaryl (optionally substituted with halogen, hydroxy, methoxy, or trifluoromethyl), or heteroarylalkyl (optionally substituted with halogen, hydroxy, methoxy, or trifluoromethyl), each R^b is independently a direct bond or a straight or branched alkylene or alkenylene chain, and R^c is a straight or branched alkylene or alkenylene chain, and where each of the above substituents is unsubstituted unless otherwise indicated.

[0049] "*N*-heterocyclyl" or "N-attached heterocyclyl" refers to a heterocyclyl radical as defined above containing at least one nitrogen and where the point of attachment of the heterocyclyl radical to the rest of the molecule is through a nitrogen atom in the heterocyclyl radical. An *N*-heterocyclyl radical is optionally substituted as described above for heterocyclyl radicals. Examples of such *N*-heterocyclyl radicals include, but are not limited to, 1-morpholinyl, 1-piperidinyl, 1-piperazinyl, 1-pyrrolidinyl, pyrazolidinyl, imidazolinyl, and imidazolidinyl.

[0050] "*C*-heterocyclyl" or "C-attached heterocyclyl" refers to a heterocyclyl radical as defined above containing at least one heteroatom and where the point of attachment of the heterocyclyl radical to the rest of the molecule is through a carbon atom in the heterocyclyl radical. A *C*-heterocyclyl radical is optionally substituted as described above for heterocyclyl radicals. Examples of such *C*-heterocyclyl radicals include, but are not limited to, 2-morpholinyl, 2- or 3- or 4-piperidinyl, 2-piperazinyl, 2- or 3-pyrrolidinyl, and the like.

[0051] "Heterocyclylalkyl" refers to a radical of the formula $-R^c$-heterocyclyl where R^c is an alkylene chain as defined above. If the heterocyclyl is a nitrogen-containing heterocyclyl, the heterocyclyl is optionally attached to the alkyl radical at the nitrogen atom. The alkylene chain of the heterocyclylalkyl radical is optionally substituted as defined above for an alkylene chain. The heterocyclyl part of the heterocyclylalkyl radical is optionally substituted as defined above for a heterocyclyl group.

[0052] "Heterocyclylalkoxy" refers to a radical bonded through an oxygen atom of the formula $-O-R^c$-heterocyclyl where R^c is an alkylene chain as defined above. If the heterocyclyl is a nitrogen-containing heterocyclyl, the heterocyclyl is optionally attached to the alkyl radical at the

nitrogen atom. The alkylene chain of the heterocyclylalkoxy radical is optionally substituted as defined above for an alkylene chain. The heterocyclyl part of the heterocyclylalkoxy radical is optionally substituted as defined above for a heterocyclyl group.

[0053] "Heteroaryl" refers to a radical derived from a 3- to 18-membered aromatic ring radical that comprises two to seventeen carbon atoms and from one to six heteroatoms selected from nitrogen, oxygen and sulfur. As used herein, the heteroaryl radical is a monocyclic, bicyclic, tricyclic or tetracyclic ring system, wherein at least one of the rings in the ring system is fully unsaturated, *i.e.*, it contains a cyclic, delocalized (4n+2) π–electron system in accordance with the Hückel theory. Heteroaryl includes fused or bridged ring systems. The heteroatom(s) in the heteroaryl radical is optionally oxidized. One or more nitrogen atoms, if present, are optionally quaternized. The heteroaryl is attached to the rest of the molecule through any atom of the ring(s). Examples of heteroaryls include, but are not limited to, azepinyl, acridinyl, benzimidazolyl, benzindolyl, 1,3-benzodioxolyl, benzofuranyl, benzooxazolyl, benzo[d]thiazolyl, benzothiadiazolyl, benzo[*b*][1,4]dioxepinyl, benzo[b][1,4]oxazinyl, 1,4-benzodioxanyl, benzonaphthofuranyl, benzoxazolyl, benzodioxolyl, benzodioxinyl, benzopyranyl, benzopyranonyl, benzofuranyl, benzofuranonyl, benzothienyl (benzothiophenyl), benzothieno[3,2-d]pyrimidinyl, benzotriazolyl, benzo[4,6]imidazo[1,2-a]pyridinyl, carbazolyl, cinnolinyl, cyclopenta[d]pyrimidinyl, 6,7-dihydro-5H-cyclopenta[4,5]thieno[2,3-d]pyrimidinyl, 5,6-dihydrobenzo[h]quinazolinyl, 5,6-dihydrobenzo[h]cinnolinyl, 6,7-dihydro-5H-benzo[6,7]cyclohepta[1,2-c]pyridazinyl, dibenzofuranyl, dibenzothiophenyl, furanyl, furanonyl, furo[3,2-c]pyridinyl, 5,6,7,8,9,10-hexahydrocycloocta[d]pyrimidinyl, 5,6,7,8,9,10-hexahydrocycloocta[d]pyridazinyl, 5,6,7,8,9,10-hexahydrocycloocta[d]pyridinyl, isothiazolyl, imidazolyl, indazolyl, indolyl, indazolyl, isoindolyl, indolinyl, isoindolinyl, isoquinolyl, indolizinyl, isoxazolyl, 5,8-methano-5,6,7,8-tetrahydroquinazolinyl, naphthyridinyl, 1,6-naphthyridinonyl, oxadiazolyl, 2-oxoazepinyl, oxazolyl, oxiranyl, 5,6,6a,7,8,9,10,10a-octahydrobenzo[h]quinazolinyl, 1-phenyl-1*H*-pyrrolyl, phenazinyl, phenothiazinyl, phenoxazinyl, phthalazinyl, pteridinyl, purinyl, pyrrolyl, pyrazolyl, pyrazolo[3,4-d]pyrimidinyl, pyridinyl, pyrido[3,2-d]pyrimidinyl, pyrido[3,4-d]pyrimidinyl, pyrazinyl, pyrimidinyl, pyridazinyl, pyrrolyl, quinazolinyl, quinoxalinyl, quinolinyl, isoquinolinyl, tetrahydroquinolinyl, 5,6,7,8-tetrahydroquinazolinyl, 5,6,7,8-tetrahydrobenzo[4,5]thieno[2,3-d]pyrimidinyl, 6,7,8,9-tetrahydro-5H-cyclohepta[4,5]thieno[2,3-d]pyrimidinyl, 5,6,7,8-tetrahydropyrido[4,5-c]pyridazinyl, thiazolyl, thiadiazolyl, triazolyl, tetrazolyl, triazinyl, thieno[2,3-d]pyrimidinyl, thieno[3,2-d]pyrimidinyl, thieno[2,3-c]pridinyl, and thiophenyl (*i.e.* thienyl). Unless stated otherwise specifically in the specification, the term "heteroaryl" is meant to

include heteroaryl radicals as defined above which are optionally substituted by one or more substituents selected from alkyl, alkenyl, alkynyl, halo, fluoroalkyl, haloalkenyl, haloalkynyl, oxo, thioxo, cyano, nitro, optionally substituted aryl, optionally substituted aralkyl, optionally substituted aralkenyl, optionally substituted aralkynyl, optionally substituted carbocyclyl, optionally substituted carbocyclylalkyl, optionally substituted heterocyclyl, optionally substituted heterocyclylalkyl, optionally substituted heteroaryl, optionally substituted heteroarylalkyl, $-R^b-OR^a$, $-R^b-OC(O)-R^a$, $-R^b-OC(O)-OR^a$, $-R^b-OC(O)-N(R^a)_2$, $-R^b-N(R^a)_2$, $-R^b-C(O)R^a$, $-R^b-C(O)OR^a$, $-R^b-C(O)N(R^a)_2$, $-R^b-O-R^c-C(O)N(R^a)_2$, $-R^b-N(R^a)C(O)OR^a$, $-R^b-N(R^a)C(O)R^a$, $-R^b-N(R^a)S(O)_tR^a$ (where t is 1 or 2), $-R^b-S(O)_tR^a$ (where t is 1 or 2), $-R^b-S(O)_tOR^a$ (where t is 1 or 2) and $-R^b-S(O)_tN(R^a)_2$ (where t is 1 or 2), where each R^a is independently hydrogen, alkyl (optionally substituted with halogen, hydroxy, methoxy, or trifluoromethyl), fluoroalkyl, cycloalkyl (optionally substituted with halogen, hydroxy, methoxy, or trifluoromethyl), cycloalkylalkyl (optionally substituted with halogen, hydroxy, methoxy, or trifluoromethyl), aryl (optionally substituted with halogen, hydroxy, methoxy, or trifluoromethyl), aralkyl (optionally substituted with halogen, hydroxy, methoxy, or trifluoromethyl), heterocyclyl (optionally substituted with halogen, hydroxy, methoxy, or trifluoromethyl), heterocyclylalkyl (optionally substituted with halogen, hydroxy, methoxy, or trifluoromethyl), heteroaryl (optionally substituted with halogen, hydroxy, methoxy, or trifluoromethyl), or heteroarylalkyl (optionally substituted with halogen, hydroxy, methoxy, or trifluoromethyl), each R^b is independently a direct bond or a straight or branched alkylene or alkenylene chain, and R^c is a straight or branched alkylene or alkenylene chain, and where each of the above substituents is unsubstituted unless otherwise indicated.

[0054] "*N*-heteroaryl" refers to a heteroaryl radical as defined above containing at least one nitrogen and where the point of attachment of the heteroaryl radical to the rest of the molecule is through a nitrogen atom in the heteroaryl radical. An *N*-heteroaryl radical is optionally substituted as described above for heteroaryl radicals.

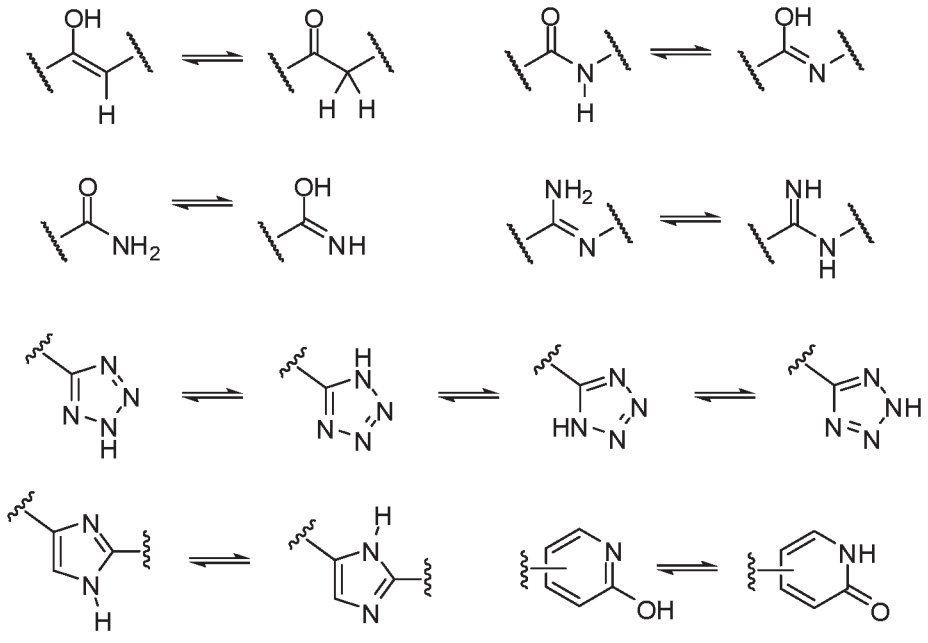
[0055] "*C*-heteroaryl" refers to a heteroaryl radical as defined above and where the point of attachment of the heteroaryl radical to the rest of the molecule is through a carbon atom in the heteroaryl radical. A *C*-heteroaryl radical is optionally substituted as described above for heteroaryl radicals.

[0056] "Heteroarylalkyl" refers to a radical of the formula $-R^c$-heteroaryl, where R^c is an alkylene chain as defined above. If the heteroaryl is a nitrogen-containing heteroaryl, the heteroaryl is optionally attached to the alkyl radical at the nitrogen atom. The alkylene chain of the heteroarylalkyl radical is optionally substituted as defined above for an alkylene chain. The heteroaryl part of the heteroarylalkyl radical is optionally substituted as defined above for a heteroaryl group.

[0057] "Heteroarylalkoxy" refers to a radical bonded through an oxygen atom of the formula –O-R^c-heteroaryl, where R^c is an alkylene chain as defined above. If the heteroaryl is a nitrogen-containing heteroaryl, the heteroaryl is optionally attached to the alkyl radical at the nitrogen atom. The alkylene chain of the heteroarylalkoxy radical is optionally substituted as defined above for an alkylene chain. The heteroaryl part of the heteroarylalkoxy radical is optionally substituted as defined above for a heteroaryl group.

[0058] The compounds disclosed herein, in some embodiments, contain one or more asymmetric centers and thus give rise to enantiomers, diastereomers, and other stereoisomeric forms that are defined, in terms of absolute stereochemistry, as (*R*)- or (*S*)-. Unless stated otherwise, it is intended that all stereoisomeric forms of the compounds disclosed herein are contemplated by this disclosure. When the compounds described herein contain alkene double bonds, and unless specified otherwise, it is intended that this disclosure includes both *E* and Z geometric isomers (*e.g., cis* or *trans*.) Likewise, all possible isomers, as well as their racemic and optically pure forms, and all tautomeric forms are also intended to be included. The term "geometric isomer" refers to *E* or Z geometric isomers (*e.g., cis* or *trans*) of an alkene double bond. The term "positional isomer" refers to structural isomers around a central ring, such as *ortho*-, *meta*-, and *para*- isomers around a benzene ring.

[0059] 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. The compounds presented herein, in certain embodiments, 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. Some examples of tautomeric equilibrium include:



[0060] The compounds disclosed herein, in some embodiments, are used in different enriched isotopic forms, e.g., enriched in the content of ^{2}H, ^{3}H, ^{11}C, ^{13}C and/or ^{14}C. In one particular embodiment, the compound is deuterated in at least one position. Such deuterated forms can be made by the procedure described in U.S. Patent Nos. 5,846,514 and 6,334,997. As described in U.S. Patent Nos. 5,846,514 and 6,334,997, deuteration can improve the metabolic stability and or efficacy, thus increasing the duration of action of drugs.

[0061] Unless otherwise stated, structures depicted herein are intended to include compounds which differ only in the presence of one or more isotopically enriched atoms. For example, compounds having the present structures except for the replacement of a hydrogen by a deuterium or tritium, or the replacement of a carbon by ^{13}C- or ^{14}C-enriched carbon are within the scope of the present disclosure.

[0062] The compounds of the present disclosure optionally contain unnatural proportions of atomic isotopes at one or more atoms that constitute such compounds. For example, the compounds may be labeled with isotopes, such as for example, deuterium (^{2}H), tritium (^{3}H), iodine-125 (^{125}I) or carbon-14 (^{14}C). Isotopic substitution with ^{2}H, ^{11}C, ^{13}C, ^{14}C, ^{15}C, ^{12}N, ^{13}N, ^{15}N, ^{16}N, ^{16}O, ^{17}O, ^{14}F, ^{15}F, ^{16}F, ^{17}F, ^{18}F, ^{33}S, ^{34}S, ^{35}S, ^{36}S, ^{35}Cl, ^{37}Cl, ^{79}Br, ^{81}Br, ^{125}I are all contemplated. In some embodiments, isotopic substitution with ^{18}F is contemplated. All isotopic variations of the compounds of the present invention, whether radioactive or not, are encompassed within the scope of the present invention.

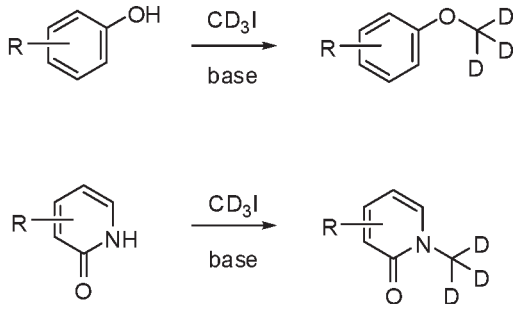
[0063] In certain embodiments, the compounds disclosed herein have some or all of the ^{1}H atoms replaced with ^{2}H atoms. The methods of synthesis for deuterium-containing compounds are known in the art and include, by way of non-limiting example only, the following synthetic methods.

[0064] Deuterium substituted compounds are synthesized using various methods such as described in: Dean, Dennis C.; Editor. Recent Advances in the Synthesis and Applications of Radiolabeled Compounds for Drug Discovery and Development. [Curr., Pharm. Des., 2000; 6(10)] **2000**, 110 pp; George W.; Varma, Rajender S. The Synthesis of Radiolabeled Compounds via Organometallic Intermediates, Tetrahedron, **1989**, 45(21), 6601-21; and Evans, E. Anthony. Synthesis of radiolabeled compounds, J. Radioanal. Chem., **1981**, 64(1-2), 9-32.

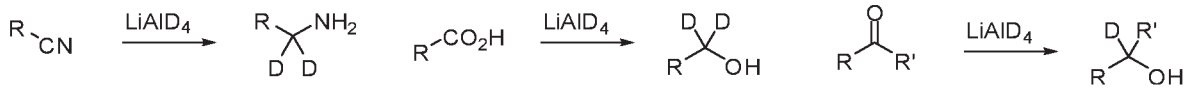
[0065] Deuterated starting materials are readily available and are subjected to the synthetic methods described herein to provide for the synthesis of deuterium-containing compounds. Large numbers of deuterium-containing reagents and building blocks are available commercially from chemical vendors, such as Aldrich Chemical Co.

[0066] Deuterium-transfer reagents suitable for use in nucleophilic substitution reactions, such as iodomethane-d_3 (CD_3I), are readily available and may be employed to transfer a deuterium-

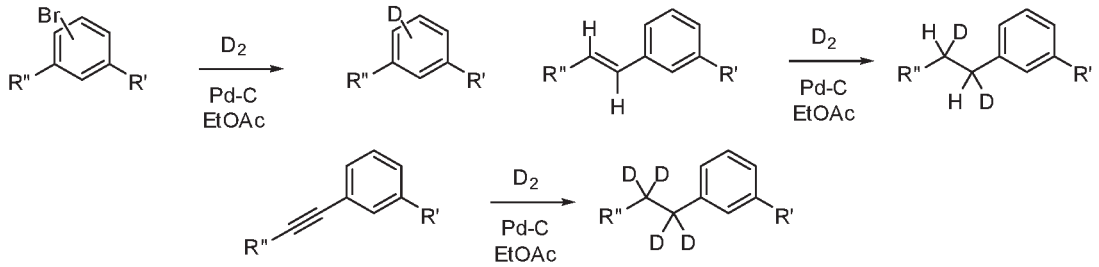
substituted carbon atom under nucleophilic substitution reaction conditions to the reaction substrate. The use of CD_3I is illustrated, by way of example only, in the reaction schemes below.



[0067] Deuterium-transfer reagents, such as lithium aluminum deuteride ($LiAlD_4$), are employed to transfer deuterium under reducing conditions to the reaction substrate. The use of $LiAlD_4$ is illustrated, by way of example only, in the reaction schemes below.



[0068] Deuterium gas and palladium catalyst are employed to reduce unsaturated carbon-carbon linkages and to perform a reductive substitution of aryl carbon-halogen bonds as illustrated, by way of example only, in the reaction schemes below.



[0069] In one embodiment, the compounds disclosed herein contain one deuterium atom. In another embodiment, the compounds disclosed herein contain two deuterium atoms. In another embodiment, the compounds disclosed herein contain three deuterium atoms. In another embodiment, the compounds disclosed herein contain four deuterium atoms. In another embodiment, the compounds disclosed herein contain five deuterium atoms. In another embodiment, the compounds disclosed herein contain six deuterium atoms. In another embodiment, the compounds disclosed herein contain more than six deuterium atoms. In another embodiment, the compound disclosed herein is fully substituted with deuterium atoms and contains no non-exchangeable ^1H hydrogen atoms. In one embodiment, the level of deuterium incorporation is determined by synthetic methods in which a deuterated synthetic building block is used as a starting material.

[0070] "Pharmaceutically acceptable salt" includes both acid and base addition salts. A pharmaceutically acceptable salt of any one of the inhibitor of cyclin-dependent kinases (CDKs) compounds

described herein is intended to encompass any and all pharmaceutically suitable salt forms. Preferred pharmaceutically acceptable salts of the compounds described herein are pharmaceutically acceptable acid addition salts and pharmaceutically acceptable base addition salts.

[0071] "Pharmaceutically acceptable acid addition salt" refers to those salts which retain the biological effectiveness and properties of the free bases, which are not biologically or otherwise undesirable, and which are formed with inorganic acids such as hydrochloric acid, hydrobromic acid, sulfuric acid, nitric acid, phosphoric acid, hydroiodic acid, hydrofluoric acid, phosphorous acid, and the like. Also included are salts that are formed with organic acids such as aliphatic mono- and dicarboxylic acids, phenyl-substituted alkanoic acids, hydroxy alkanoic acids, alkanedioic acids, aromatic acids, aliphatic and. aromatic sulfonic acids, etc. and include, for example, acetic acid, trifluoroacetic acid, propionic acid, glycolic acid, pyruvic acid, oxalic acid, maleic acid, malonic acid, succinic acid, fumaric acid, tartaric acid, citric acid, benzoic acid, cinnamic acid, mandelic acid, methanesulfonic acid, ethanesulfonic acid, p-toluenesulfonic acid, salicylic acid, and the like. Exemplary salts thus include sulfates, pyrosulfates, bisulfates, sulfites, bisulfites, nitrates, phosphates, monohydrogenphosphates, dihydrogenphosphates, metaphosphates, pyrophosphates, chlorides, bromides, iodides, acetates, trifluoroacetates, propionates, caprylates, isobutyrates, oxalates, malonates, succinate suberates, sebacates, fumarates, maleates, mandelates, benzoates, chlorobenzoates, methylbenzoates, dinitrobenzoates, phthalates, benzenesulfonates, toluenesulfonates, phenylacetates, citrates, lactates, malates, tartrates, methanesulfonates, and the like. Also contemplated are salts of amino acids, such as arginates, gluconates, and galacturonates (see, for example, Berge S.M. et al., "Pharmaceutical Salts," *Journal of Pharmaceutical Science,* 66:1-19 (1997)). Acid addition salts of basic compounds are, in some embodiments, prepared by contacting the free base forms with a sufficient amount of the desired acid to produce the salt according to methods and techniques with which a skilled artisan is familiar.

[0072] "Pharmaceutically acceptable base addition salt" refers to those salts that retain the biological effectiveness and properties of the free acids, which are not biologically or otherwise undesirable. These salts are prepared from addition of an inorganic base or an organic base to the free acid. Pharmaceutically acceptable base addition salts are, in some embodiments, formed with metals or amines, such as alkali and alkaline earth metals or organic amines. Salts derived from inorganic bases include, but are not limited to, sodium, potassium, lithium, ammonium, calcium, magnesium, iron, zinc, copper, manganese, aluminum salts and the like. Salts derived from organic bases include, but are not limited to, salts of primary, secondary, and tertiary amines, substituted amines including naturally occurring substituted amines, cyclic amines and basic ion exchange resins, for example, isopropylamine, trimethylamine, diethylamine, triethylamine, tripropylamine,

ethanolamine, diethanolamine, 2-dimethylaminoethanol, 2-diethylaminoethanol, dicyclohexylamine, lysine, arginine, histidine, caffeine, procaine, *N,N*-dibenzylethylenediamine, chloroprocaine, hydrabamine, choline, betaine, ethylenediamine, ethylenedianiline, *N*-methylglucamine, glucosamine, methylglucamine, theobromine, purines, piperazine, piperidine, N-ethylpiperidine, polyamine resins and the like. See Berge et al., supra.

[0073] "Pharmaceutically acceptable solvate" refers to a composition of matter that is the solvent addition form. In some embodiments, solvates contain either stoichiometric or non-stoichiometric amounts of a solvent, and are formed during the process of making 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. The compounds provided herein optionally exist in either unsolvated as well as solvated forms.

[0074] 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.

[0075] As used herein, “treatment” or “treating,” or “palliating” or “ameliorating” are used interchangeably. These terms refer to an approach for obtaining beneficial or desired results including but not limited to therapeutic benefit and/or a prophylactic benefit. By “therapeutic benefit” is meant eradication or amelioration of the underlying disorder being treated. Also, a therapeutic benefit is achieved with the eradication or amelioration of one or more of the physiological symptoms associated with the underlying disorder such that an improvement is observed in the patient, notwithstanding that the patient is still afflicted with the underlying disorder. For prophylactic benefit, the compositions are, in some embodiments, administered to a patient at risk of developing a particular disease, or to a patient reporting one or more of the physiological symptoms of a disease, even though a diagnosis of this disease has not been made.

Cyclin-Dependent Kinases

[0076] Cyclin-dependent kinases (CDKs) are a family of serine/threonine protein kinases that are known to function in the processes of cell cycle regulation, metabolism, gene transcription, RNA processing, and DNA repair, with each CDK playing a distinct role (Malumbres, M., 2014, Genome Biol. 15(6), 122-132; Lim et al., 2013, Development 140, 3079-3093). Inhibition of CDKs has long been of therapeutic interest in the treatment of conditions characterized by cellular hyperproliferation,

such as cancer, psoriasis, and fungal infections (Coleman, K. G. et al., 1997, Annual Reports in Medicinal Chemistry 32, 171-179).

[0077] CDKs are characterized by as being dependent on one or more separate catalytic cyclin subunits in order to carry out specific functions (Malumbres, 2014). Structurally, CDKs comprise a conserved catalytic core containing an ATP-binding pocket, a cyclin binding domain, and an activating T-loop motif (Coleman, 1997; Enke et al., 1999, J. Biol. Chem. 274(4), 1949-1956).

[0078] Human cells are known to have at least 20 CDKs and 29 cyclins, which can be grouped into 8 subfamilies (Lim, 2013; Cao et al., 2014, BMC Evol. Biol. 14, 10-26). Therapies known in the art include selective inhibition of specific CDKs.

[0079] CDK7 and CDK9 are part of the subfamily of transcriptional CDKs which regulate gene transcription via the phosphorylation of the carboxy-terminal domain of RNA polymerase II (Lücking, U., 2017, ChemMedChem. 12(21), 1776-1793). Inhibitors of CDK7 and CDK9 are recognized in the art as being therapeutically beneficial against various types of cancers.

[0080] CDK7 is known to be required for activity-dependent neuronal gene expression, synaptic plasticity, and long-term memory (He et al., 2017, Front. Mol. Neurosci. 10, 365-377). CDK7 inhibition is known to suppress rheumatoid arthritis inflammation via blocking NF-kB activation and IL-1β/IL-6 secretion (Hong et al., 2017, J. Cell. Mol. Med. 22, 1292-1301), and has been shown to disrupt the cell cycle of high-grade glioma (Greenall et al., 2017, Oncogenesis 6(5), e336). The CDK7 inhibitor THZ1 has been shown to significantly affect transcription in T cell leukemia, neuroblastoma, small-cell lung cancer and triple-negative breast cancer cells in vitro (Gao et al., 2017, Cell Chem. Biol. 25, 1-8; Kwiatkowski et al., 2014, Nature 511(7511), 616-620). When screened against a panel of 1,151 cancer cell lines, a THZ1 concentration less than 200nM exhibited an IC50 in 52% of those lines (Kwiatkowski, 2014, see Table 3a).

[0081] CDK9 is known to regulate the expression of antiapoptotic proteins for the survival of cancer cells (Pang et al., 2017, Cancer Med. 6(10), 2398-2409) and is known to regulate the DNA damage response in complex with cyclin-K (Lim, 2013). Inhibitors of CDK9 have been shown to repress transcription of genes associated with B-cell lymphoma, the most common form of non-Hodgkin lymphoma (Dey et al., 2017, Sci. Rep. 7(1), 18007), hepatocellular carcinoma (Pang, 2017), NUT midline carcinoma (Brägelmann et al., 2017, Cell Rep. 20(12), 2833-2845), ovarian cancer, epithelial carcinoma, colorectal carcinoma, cervical carcinoma, prostate adenocarcinoma, breast adenocarcinoma, and pancreatic carcinoma (Lam et al., 2014, Oncotarget 5, 7691-7704).

[0082] CDK12 and CDK13 are transcription-associated CDKs, and are known to regulate RNA polymerase II transcription in complex with cyclin K (Lim, 2013), as well as axonal and

transcriptional elongation (Chen et al., 2014, Exp. Neurol. 261, 10-21; Paculová et al., 2017, Cell Div. 12, 7-17).

[0083] It has been suggested that CDK12 has oncogenic properties, and is mutated or overexpressed in various types of cancer, leading to dysregulation of cell proliferation (Paculová, 2017). CDK12 inhibitors have been found to reduce gene expression in BRCA cells (Johnson et al., 2016, Cell Rep. 17(9), 2367-2381). Mutations of CDK12 have been shown to disrupt DNA repair, contributing to hyperproliferation and the pathogenesis of breast tumor cells (Tien et al., 2017, Nucleic Acids Res. 45(11), 6698-6716). It is estimated that CDK12 mutations are present in 13% of breast cancers and 5% of ovarian cancers (Tien, 2017; Cerami et al., 2012, Cancer Discov. 2, 401–404; Cancer Genome Atlas Research Network, 2011, Nature, 474, 609–615; Kandoth et al., 2013, Nature 502, 333–339; Cancer Genome Atlas Network, 2012, Nature 490, 61–70).

[0084] CDK13 is known to regulate processes associated with growth signaling (Greifenberg et al., 2016, Cell Rep. 14, 320-331). CDK13 mutations affecting the protein kinase domain have been linked to congenital heart disease, developmental delay and intellectual disability (Hamilton et al., 2017, J. Med. Genet. 55(1), 28-38). CDK13 is known to interact with the splicing factor SRSF1 and regulate alternative splicing of HIV mRNA (Berro et al., 2008, J. Virol. 82, 7155-7166).

[0085] CDK inhibitory compounds have been described in the literature. See, for example: Gao et al., 2018, Cell Chem. Biol. 25(2), 135-142; WO 2017/044858; WO 2016/210296; WO 2016/201370; Ficarro et al., 2016, Anal. Chem. 88(24), 12248-12254; WO 2016/160617; Zhang et al., 2016, Nature Chem. Biol. 12(10), 876-884; WO 2016/105528; WO 2015/058126; and WO 2015/058163. Other examples include: WO 2015/124941; Ali et al., 2009, Cancer Res. 69(15), 6208-6215; WO 2016/193939; Bajrami et al., 2014, Cancer Res. 74(1), 287-297; Li et al., 2017, Cancer Res. 77(14), 3834–3845; Cayrol et al., 2017, Nature Commun. 8:14290, 1–11; Johnson et al., 2016, Cell Reports 17(9), 2367-2381; Kalan et al., 2017, Cell Reports 21(2), 467-481; Christensen et al., 2014, Cancer Cell 26(6), 909-922; Iniguez et al., 2018, Cancer Cell 33(2), 202-216; Mertins et al., 2016, Nature 534(7605), 55–62; Nagaraja et al., 2017, Cancer Cell 31(5), 635-652; Naidoo et al., 2017, Mol. Cancer Ther. 17(1), 306-315; Paculova et al., 2017, Cell Div. 12:7, 1-10; and Evan et al., 2017, Clin. Cancer Res. 23(7), 1647-1655.

[0086] Based on the role of CDKs in the processes of cell cycle regulation, metabolism, gene transcription, RNA processing, and DNA repair, compounds which alter CDKs activity are considered to be useful in treating or preventing various disorders, including cancer. In some embodiments, described herein is a small molecule inhibitor of cyclin-dependent kinases (CDKs). In some embodiments, described herein is a pharmaceutical composition comprising a small molecule inhibitor of cyclin-dependent kinases (CDKs). In other embodiments, a small molecule inhibitor of

cyclin-dependent kinases (CDKs) is used to treat or prevent a disease or condition in a subject in need thereof.

[0087] In some embodiments, a heteroaromatic CDK inhibitory compound as described herein is used to treat or prevent cancer in a subject in need thereof. In some embodiments, a pharmaceutical composition comprising a heteroaromatic CDK inhibitory compound as described herein is used to treat or prevent cancer in a subject in need thereof. In some embodiments, disclosed herein is a method of treating cancer comprising administering to a subject in need thereof a therapeutically effective amount of a heteroaromatic CDK inhibitory compound as described herein. In some embodiments, disclosed herein is a method of treating cancer comprising administering to a subject in need thereof a therapeutically effective amount of a pharmaceutical composition comprising a heteroaromatic CDK inhibitory compound as described herein. In some embodiments, disclosed herein is a method of treating cancer comprising administering to a subject having been previously diagnosed with cancer a therapeutically effective amount of a heteroaromatic CDK inhibitory compound as described herein.

[0088] In some embodiments, a heteroaromatic CDK inhibitory compound is a heteroaromatic CDK7, CDK9, CDK12, and CDK13 inhibitory compound. In some embodiments, a heteroaromatic CDK inhibitory compound is a heteroaromatic CDK7 inhibitory compound. In some embodiments, a heteroaromatic CDK inhibitory compound is a heteroaromatic CDK9 inhibitory compound. In some embodiments, a heteroaromatic CDK inhibitory compound is a heteroaromatic CDK12 inhibitory compound. In some embodiments, a heteroaromatic CDK inhibitory compound is a heteroaromatic CDK13 inhibitory compound. In some embodiments, a heteroaromatic CDK inhibitory compound is a heteroaromatic CDK7 and CDK9 inhibitory compound. In some embodiments, a heteroaromatic CDK inhibitory compound is a heteroaromatic CDK7 and CDK12 inhibitory compound. In some embodiments, a heteroaromatic CDK inhibitory compound is a heteroaromatic CDK7 and CDK13 inhibitory compound. In some embodiments, a heteroaromatic CDK inhibitory compound is a heteroaromatic CDK9 and CDK12 inhibitory compound. In some embodiments, a heteroaromatic CDK inhibitory compound is a heteroaromatic CDK9 and CDK13 inhibitory compound. In some embodiments, a heteroaromatic CDK inhibitory compound is a heteroaromatic CDK12 and CDK13 inhibitory compound. In some embodiments, a heteroaromatic CDK inhibitory compound is a heteroaromatic CDK7, CDK9, and CDK12 inhibitory compound.

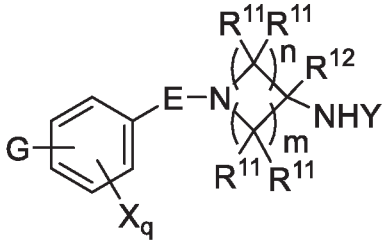
[0089] In some embodiments, a heteroaromatic CDK inhibitory compound is a heteroaromatic CDK7, CDK9, and CDK13 inhibitory compound. In some embodiments, a heteroaromatic CDK inhibitory compound is a heteroaromatic CDK7, CDK12, and CDK13 inhibitory compound. In some

embodiments, a heteroaromatic CDK inhibitory compound is a heteroaromatic CDK9, CDK12, and CDK13 inhibitory compound.

Heteroaromatic CDK Inhibitory Compounds

[0090] In one aspect, provided herein is a heteroaromatic CDK inhibitory compound.

[0091] One embodiment provides a compound, or pharmaceutically acceptable salt or solvate thereof, having the structure of Formula (I):

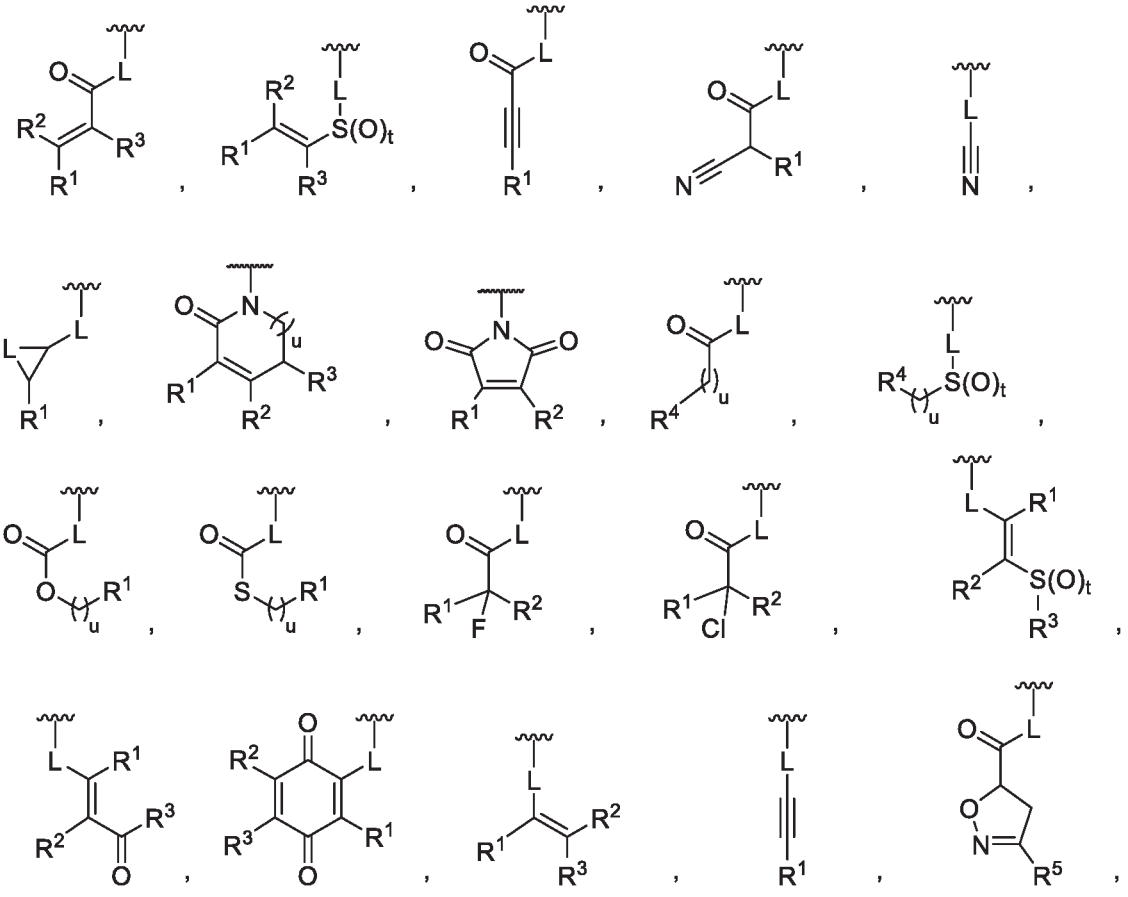


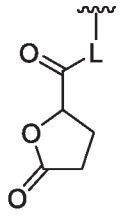
(I)

wherein,

E is selected from a bond, $-SO_2-$, -C(O)-, $-CH_2-$, $-CH(R^4)-$, or $-C(R^4)_2-$;

G is selected from a group having the structure:

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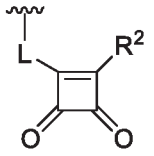
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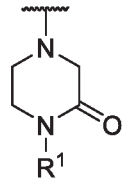
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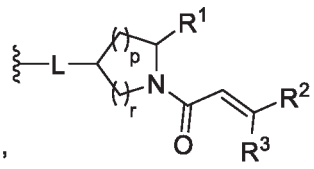
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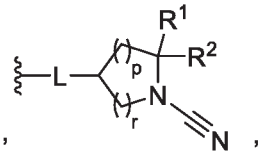
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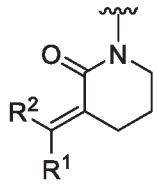
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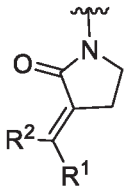

;

wherein,

L is O, NH, N(optionally substituted C1-C4 alkyl), or -NH-CH_2-* wherein the * denotes the point of attachment to the phenyl ring;

t is 0, 1, or 2;

u is 1, or 2;

p is 0, 1, or 2;

r is 0, 1, or 2;

R^1 is selected from hydrogen, optionally substituted C1-C4 alkyl, or optionally substituted heterocyclylalkyl;

R^2 is selected from hydrogen, or optionally substituted C1-C4 alkyl;

R^3 is selected from hydrogen, -CN, or optionally substituted C1-C4 alkyl;

each R^4 is independently selected from optionally substituted C1-C4 alkyl, or optionally substituted heterocyclylalkyl;

R^5 is optionally substituted C1-C4 alkyl, or optionally substituted heterocyclylalkyl;

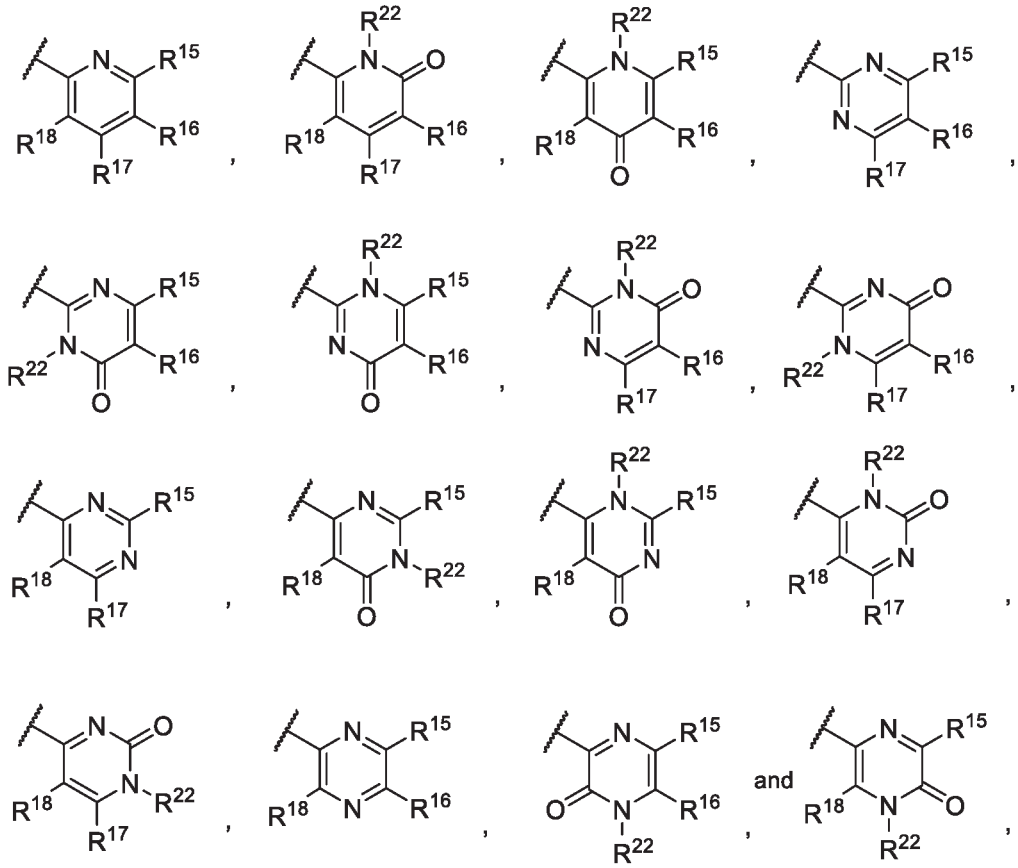
each R^{11} is independently hydrogen, halogen, optionally substituted C1-C6 alkyl, -OH, optionally substituted C1-C4 alkoxy, or two R^{11} groups on the same carbon atom form an oxo;

R^{12} is hydrogen or optionally substituted C1-C4 alkyl;

q is 0, 1, 2, or 3; n is 0, 1, 2, or 3; m is 0, 1, 2, or 3;

each X is independently halogen, optionally substituted C1-C4 alkyl, optionally substituted C1-C4 alkoxy, optionally substituted aminoalkyl, optionally substituted cycloalkyl, optionally substituted heterocyclyl, optionally substituted aryl, or optionally substituted heteroaryl;

Y is a group selected from:



wherein,

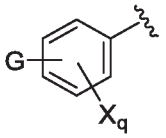
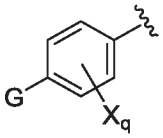
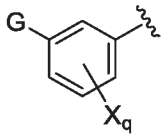
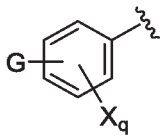
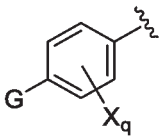
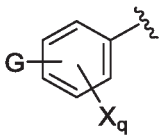
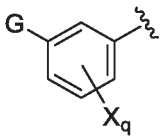
R^{15} is selected from hydrogen, halogen, -CN, optionally substituted alkyl, optionally substituted fluoroalkyl, optionally substituted alkoxy, optionally substituted cycloalkyl, optionally substituted heterocyclyl, optionally substituted cycloalkylalkyl, optionally substituted cycloalkyl-O-, optionally substituted aryl, optionally substituted aralkyl, optionally substituted aryloxy, optionally substituted aralkyloxy, optionally substituted heteroaryloxy, optionally substituted heteroaralkyloxy, $-OR^{22}$, $-N(R^{22})_2$, $-SO_2R^{21}$, $-N(R^{22})SO_2R^{21}$, $-SO_2N(R^{22})_2$, $-N(R^{22})SO_2N(R^{22})_2$, $-CON(R^{22})_2$, $-N(R^{22})CO_2R^{21}$, $-N(R^{22})CON(R^{22})_2$, $-N(R^{22})COR^{21}$, $-OC(O)N(R^{22})_2$, $-OSO_2N(R^{22})_2$, or $-N(R^{22})SO_3R^{21}$;

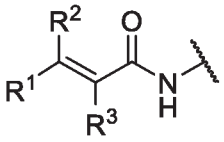
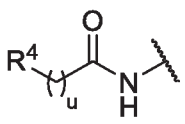
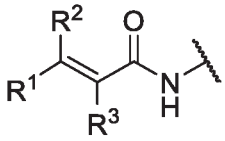
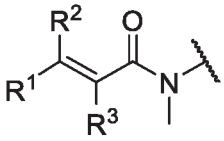
R^{16} is selected from hydrogen, halogen, -CN, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted fluoroalkyl, optionally substituted alkoxy, optionally substituted cycloalkyl, optionally substituted heterocyclyl, optionally substituted cycloalkylalkyl, optionally substituted cycloalkyl-O-, optionally substituted aryl, optionally substituted aralkyl, optionally substituted heteroaryl, optionally substituted heteroaralkyl, optionally substituted aryloxy, optionally substituted aralkyloxy, optionally substituted heteroaryloxy, optionally substituted heteroaralkyloxy, $-OR^{22}$, $-N(R^{22})_2$, $-SO_2R^{21}$, $-N(R^{22})SO_2R^{21}$, $-SO_2N(R^{22})_2$, $-N(R^{22})SO_2N(R^{22})_2$, $-CON(R^{22})_2$, $-N(R^{22})CO_2R^{21}$, $-N(R^{22})CON(R^{22})_2$, $-N(R^{22})COR^{21}$, $-OC(O)N(R^{22})_2$, $-OSO_2N(R^{22})_2$, or $-N(R^{22})SO_3R^{21}$;

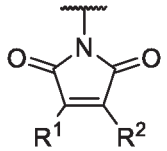
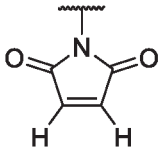
R^{17} is selected from hydrogen, halogen, -CN, optionally substituted alkyl, optionally substituted fluoroalkyl, optionally substituted alkoxy, optionally substituted cycloalkyl, optionally substituted heterocyclyl, optionally substituted cycloalkylalkyl, optionally substituted cycloalkyl-O-, optionally substituted aryl, optionally substituted aralkyl, optionally substituted aryloxy, optionally substituted aralkyloxy, optionally substituted heteroaryloxy, optionally substituted heteroaralkyloxy, $-OR^{22}$, $-N(R^{22})_2$, $-SO_2R^{21}$, $-N(R^{22})SO_2R^{21}$, $-SO_2N(R^{22})_2$, $-N(R^{22})SO_2N(R^{22})_2$, $-CON(R^{22})_2$, $-N(R^{22})CO_2R^{21}$, $-N(R^{22})CON(R^{22})_2$, $-N(R^{22})COR^{21}$, $-OC(O)N(R^{22})_2$, $-OSO_2N(R^{22})_2$, or $-N(R^{22})SO_3R^{21}$;

each R^{21} is independently selected from alkyl, cycloalkyl, cycloalkylalkyl, aryl, aralkyl, heterocyclyl, heterocyclylalkyl, heteroaryl, or heteroarylalkyl; and

each R^{22} is independently selected from hydrogen, alkyl, cycloalkyl, cycloalkylalkyl, aryl, aralkyl, heterocyclyl, heterocyclylalkyl, heteroaryl, or heteroarylalkyl.

[0092] In some embodiments,  is  or . In some embodiments,  is . In some embodiments,  is .

[0093] In some embodiments, G is  or . In some embodiments, G is . In some embodiments, G is .

[0094] In some embodiments, G is . In some embodiments, G is .

[0095] In some embodiments, R^3 is hydrogen or –CN.

[0096] In some embodiments, L is O, NH, or N(optionally substituted C1-C4 alkyl);

[0097] In some embodiments, L is NH. In some embodiments, L is NCH_3.

[0098] In some embodiments, t is 2.

[0099] In some embodiments, q is 0, 1, or 2.

[00100] In some embodiments, q is 0, or 1.

[00101] In some embodiments, q is 0.

[00102] In some embodiments, X is a halogen.

[00103] In some embodiments, R^2 is hydrogen.

[00104] In some embodiments, R^3 is hydrogen.

[00105] In some embodiments, R^2 and R^3 is hydrogen.

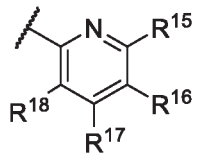
[00106] In some embodiments, R^1 is hydrogen. In some embodiments, R^1 is optionally substituted C1-C4 alkyl. In some embodiments, R^1 is optionally substituted C1-C2 alkyl. In some embodiments, R^1 is optionally substituted C1 alkyl. In some embodiments, the C1 alkyl is substituted with an optionally substituted amino group. In some embodiments, the optionally substituted amino group is a dimethylamino.

[00107] In some embodiments, R^1 is $–CH_2-N(Me)_2$.

[00108] In some embodiments, R^1 is optionally substituted heterocyclylalkyl. In some embodiments, the optionally substituted heterocyclylalkyl comprises an optionally substituted C1 alkyl. In some embodiments, the optionally substituted heterocyclylalkyl comprises an optionally substituted N-linked heterocyclyl. In some embodiments, the optionally substituted N-linked heterocyclyl is an N-linked pyrrolidine or piperidine.

[00109] In some embodiments, n is 1 and m is 1. In some embodiments, n is 1 and m is 2. In some embodiments, n is 1 and m is 3.

[00110] In some embodiments, Y is selected from: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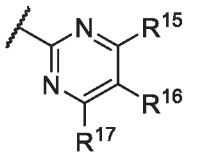
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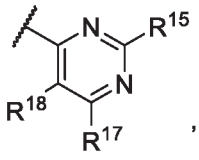
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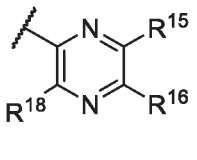
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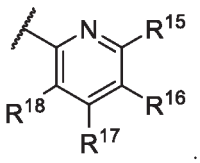
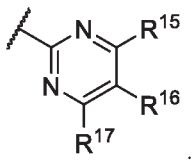
[00111] In some embodiments, Y is:

. In some embodiments, Y is:

.

[00112] In some embodiments, R^{15} is selected from hydrogen, halogen, -CN, and optionally substituted alkyl. In some embodiments, R^{15} is hydrogen.

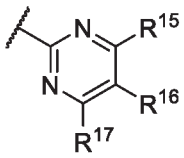
[00113] In some embodiments, R^{16} is selected from hydrogen, halogen, -CN, optionally substituted alkyl, optionally substituted fluoroalkyl, optionally substituted alkoxy, optionally substituted cycloalkyl, optionally substituted heterocyclyl, optionally substituted cycloalkylalkyl, optionally substituted cycloalkyl-O-, optionally substituted aryl, optionally substituted aralkyl, optionally substituted heteroaryl, optionally substituted heteroaralkyl, optionally substituted aryloxy, optionally substituted aralkyloxy, optionally substituted heteroaryloxy, optionally substituted

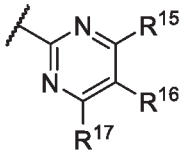
heteroaralkyloxy, -OR^{22}, -$N(R^{22})_2$, -SO_2R^{21}, -$N(R^{22})SO_2R^{21}$, -$SO_2N(R^{22})_2$, –$N(R^{22})SO_2N(R^{22})_2$, -$CON(R^{22})_2$, -$N(R^{22})CO_2R^{21}$, -$N(R^{22})CON(R^{22})_2$, -$N(R^{22})COR^{21}$, -$OC(O)N(R^{22})_2$, -$OSO_2N(R^{22})_2$, or -$N(R^{22})SO_3R^{21}$.

[00114] In some embodiments, L is O, NH, or N(optionally substituted C1-C4 alkyl); and R^{16} is selected from hydrogen, halogen, -CN, optionally substituted alkyl, optionally substituted fluoroalkyl, optionally substituted alkoxy, optionally substituted cycloalkyl, optionally substituted heterocyclyl, optionally substituted cycloalkylalkyl, optionally substituted cycloalkyl-O-, optionally substituted aryl, optionally substituted aralkyl, optionally substituted heteroaryl, optionally substituted heteroaralkyl, optionally substituted aryloxy, optionally substituted aralkyloxy, optionally substituted heteroaryloxy, optionally substituted heteroaralkyloxy, -OR^{22}, -$N(R^{22})_2$, -SO_2R^{21}, -$N(R^{22})SO_2R^{21}$, -$SO_2N(R^{22})_2$, –$N(R^{22})SO_2N(R^{22})_2$, -$CON(R^{22})_2$, -$N(R^{22})CO_2R^{21}$, -$N(R^{22})CON(R^{22})_2$, -$N(R^{22})COR^{21}$, -$OC(O)N(R^{22})_2$, -$OSO_2N(R^{22})_2$, or -$N(R^{22})SO_3R^{21}$.

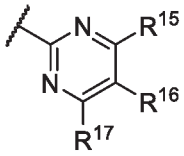
[00115] In some embodiments, R^{16} is selected from hydrogen, halogen, -CN, and optionally substituted alkyl. In some embodiments, R^{16} is hydrogen.

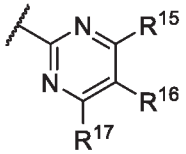
[00116] In some embodiments, R^{16} is selected from optionally substituted alkyl, optionally substituted alkenyl, or optionally substituted alkynyl. In some embodiments, R^{16} is selected from optionally substituted alkynyl.

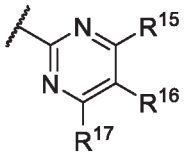
[00117] In some embodiments, Y is: , and R^{16} is not hydrogen.

[00118] In some embodiments, Y is: , and R^{16} is halogen.

[00119] In some embodiments, Y is: , and R^{16} is selected from optionally substituted alkyl, optionally substituted alkenyl, or optionally substituted alkynyl.

[00120] In some embodiments, Y is: , R^{15} is hydrogen, R^{16} is selected from optionally substituted alkynyl, and R^{17} is hydrogen or optionally substituted alkoxy.

[00121] In some embodiments, Y is:  ; R^{15} is hydrogen, R^{16} is selected from halogen, -CN, optionally substituted alkyl, optionally substituted fluoroalkyl, optionally substituted alkenyl, optionally substituted alkynyl, and R^{17} is hydrogen or optionally substituted alkoxy.

[00122] In some embodiments, n is 1 and m is 2; Y is:  ; R^{15} is hydrogen, R^{16} is selected from halogen, -CN, optionally substituted alkyl, optionally substituted fluoroalkyl, optionally substituted alkenyl, optionally substituted alkynyl, and R^{17} is hydrogen or optionally substituted alkoxy.

[00123] In some embodiments, R^{17} is selected from hydrogen, halogen, -CN, and optionally substituted alkyl. In some embodiments, R^{17} is hydrogen.

[00124] In some embodiments, R^{18} is selected from hydrogen, halogen, -CN, and optionally substituted alkyl. In some embodiments, R^{18} is hydrogen.

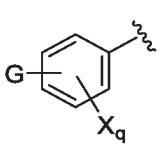
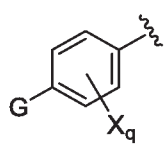
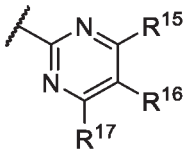
[00125] In some embodiments, R^{15} and R^{16} are hydrogen. In some embodiments, R^{17} and R^{18} are hydrogen.

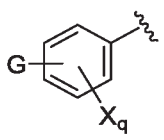
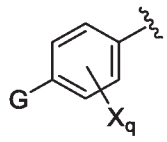
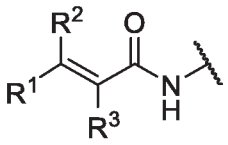
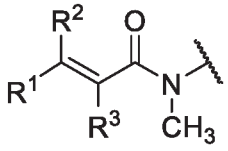
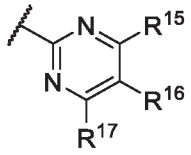
[00126] In some embodiments, R^{15} and R^{17} are hydrogen.

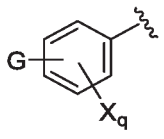
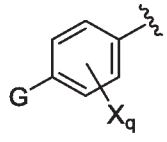
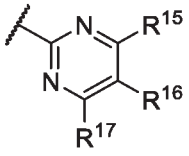
[00127] In some embodiments, E is a bond. In some embodiments, E is $-SO_2-$. In some embodiments, E is -C(O)-. In some embodiments, E is $–CH_2-$. In some embodiments, E is $-CH(R^4)-$. In some embodiments, E is $-C(R^4)_2-$.

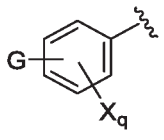
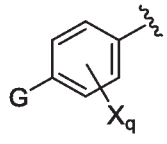
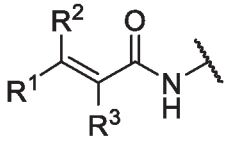
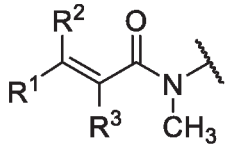
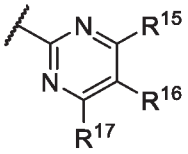
[00128] In some embodiments, R^{11} is hydrogen. In some embodiments, n is 1 and m is 2; and R^{11} is hydrogen.

[00129] In some embodiments, R^{12} is hydrogen. In some embodiments, R^{12} is optionally substituted C1-C4 alkyl.

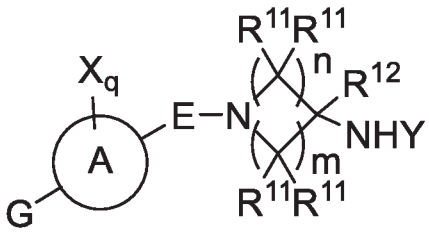
[00130] One embodiment provides the compound of Formula (I), or pharmaceutically acceptable salt or solvate thereof, wherein  is  ; Y is:  ; R^{11} and R^{12} are hydrogen; n is 1 and m is 2; and E is -C(O)-.

[00131] One embodiment provides the compound of Formula (I), or pharmaceutically acceptable salt or solvate thereof, wherein  is  ; G is  , or  ; Y is:  ; R^{11} and R^{12} are hydrogen; n is 1 and m is 2; and E is -C(O)-.

[00132] One embodiment provides the compound of Formula (I), or pharmaceutically acceptable salt or solvate thereof, wherein  is  ; Y is:  ; R^{15} is hydrogen, R^{16} is selected from halogen, -CN, optionally substituted alkyl, optionally substituted fluoroalkyl, optionally substituted alkynyl, and R^{17} is hydrogen or optionally substituted alkoxy; R^{11} and R^{12} are hydrogen; n is 1 and m is 2; and E is -C(O)-.

[00133] One embodiment provides the compound of Formula (I), or pharmaceutically acceptable salt or solvate thereof, wherein  is  ; q is 0; G is  , or  ; R^1, R^2 and R^3 are each hydrogen; Y is:  ; R^{15} is hydrogen, R^{16} is selected from halogen, -CN, optionally substituted alkyl, optionally substituted fluoroalkyl, optionally substituted alkynyl, and R^{17} is hydrogen or optionally substituted alkoxy; R^{11} and R^{12} are hydrogen; n is 1 and m is 2; and E is -C(O)-.

[00134] One embodiment provides a compound, or pharmaceutically acceptable salt or solvate thereof, having the structure of Formula (II):



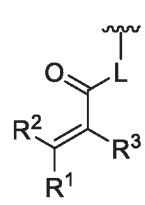
(II)

wherein,

ring A is a monocyclic heteroaryl;

E is selected from a bond, -SO_2-, -C(O)-, –CH_2-, -$CH(R^4)$-, or -$C(R^4)_2$-;

G is selected from a group having the structure: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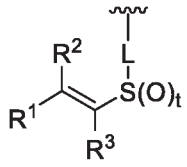
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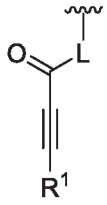
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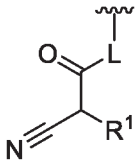
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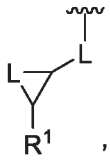
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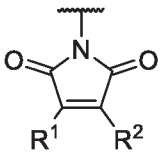
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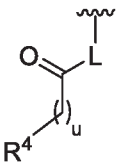
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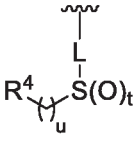
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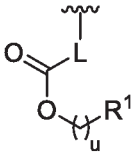
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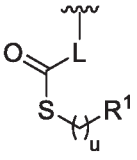
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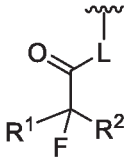
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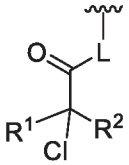
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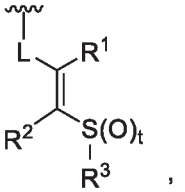
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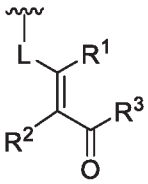
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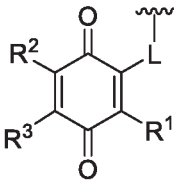
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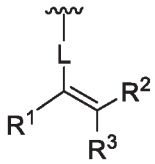
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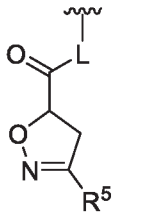
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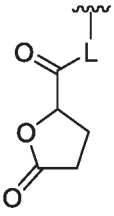
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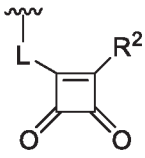
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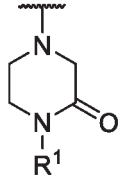
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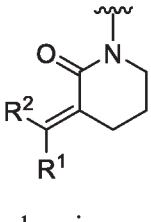
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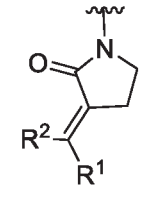
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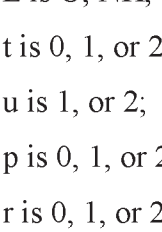

, or

;

wherein,

L is O, NH, or N(optionally substituted C1-C4 alkyl);

t is 0, 1, or 2;

u is 1, or 2;

p is 0, 1, or 2;

r is 0, 1, or 2;

R^1 is selected from hydrogen, optionally substituted C1-C4 alkyl, or optionally substituted heterocyclylalkyl;

R^2 is selected from hydrogen, or optionally substituted C1-C4 alkyl;

R^3 is selected from hydrogen, -CN, or optionally substituted C1-C4 alkyl;

each R^4 is independently selected from optionally substituted C1-C4 alkyl, or optionally substituted heterocyclylalkyl;

R^5 is optionally substituted C1-C4 alkyl, or optionally substituted heterocyclylalkyl;

each R^{11} is independently hydrogen, halogen, optionally substituted C1-C6 alkyl, -OH, optionally substituted C1-C4 alkoxy, or two R^{11} groups on the same carbon atom form an oxo;

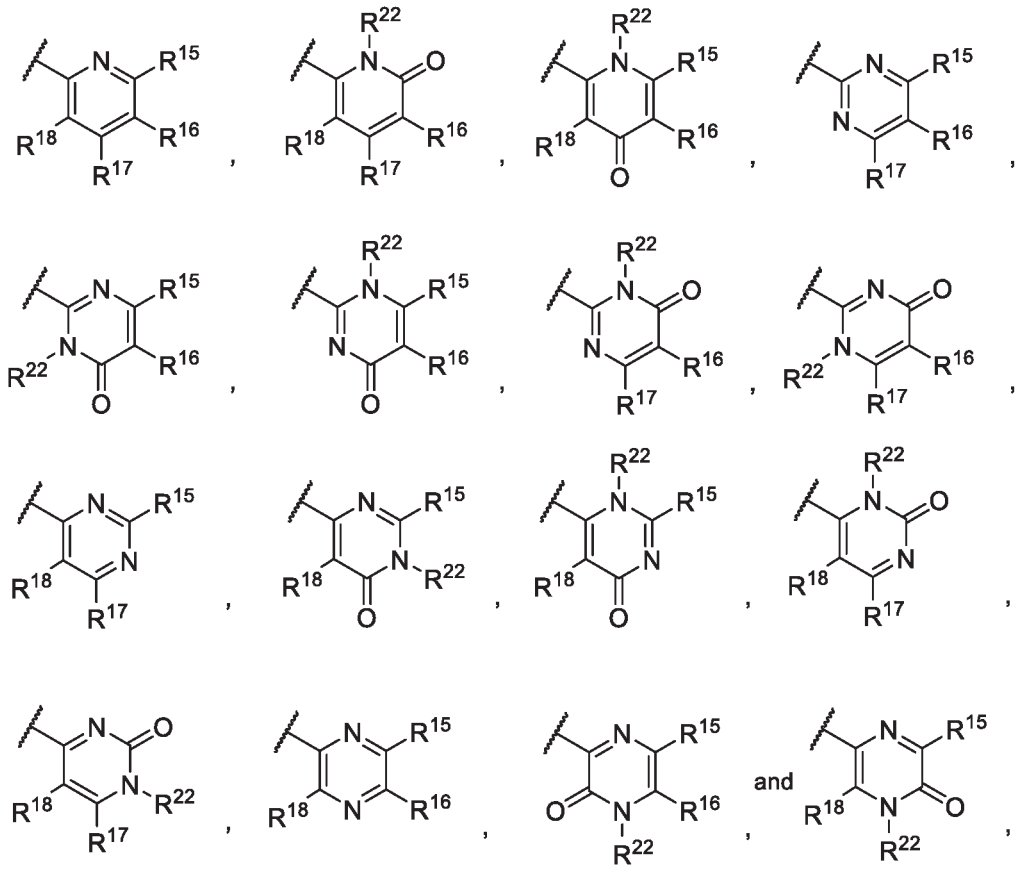
R^{12} is hydrogen or optionally substituted C1-C4 alkyl;

q is 0, 1, 2, or 3;

n is 0, 1, 2, or 3; m is 0, 1, 2, or 3;

each X is independently halogen, optionally substituted C1-C4 alkyl, optionally substituted C1-C4 alkoxy, optionally substituted aminoalkyl, optionally substituted cycloalkyl, optionally substituted heterocyclyl, optionally substituted aryl, or optionally substituted heteroaryl;

Y is a group selected from:



wherein,

R^{15} is selected from hydrogen, halogen, -CN, optionally substituted alkyl, optionally substituted fluoroalkyl, optionally substituted alkoxy, optionally substituted cycloalkyl, optionally substituted heterocyclyl, optionally substituted cycloalkylalkyl, optionally substituted cycloalkyl-O-, optionally substituted aryl, optionally substituted aralkyl, optionally substituted heteroaryl, optionally substituted heteroaralkyl, optionally substituted aryloxy, optionally substituted aralkyloxy, optionally substituted heteroaryloxy, optionally substituted heteroaralkyloxy, $-OR^{22}$, $-N(R^{22})_2$, $-SO_2R^{21}$, $-N(R^{22})SO_2R^{21}$, $-SO_2N(R^{22})_2$, $–N(R^{22})SO_2N(R^{22})_2$, $-CON(R^{22})_2$, $-N(R^{22})CO_2R^{21}$, $-N(R^{22})CON(R^{22})_2$, $-N(R^{22})COR^{21}$, $-OC(O)N(R^{22})_2$, $-OSO_2N(R^{22})_2$, or $-N(R^{22})SO_3R^{21}$;

R^{16} is selected from hydrogen, halogen, -CN, optionally substituted alkyl, optionally substituted fluoroalkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted alkoxy, optionally substituted cycloalkyl, optionally substituted heterocyclyl, optionally substituted cycloalkylalkyl, optionally substituted cycloalkyl-O-, optionally substituted aryl, optionally substituted aralkyl, optionally substituted heteroaryl, optionally substituted heteroaralkyl, optionally substituted aryloxy, optionally substituted aralkyloxy, optionally substituted heteroaryloxy, optionally substituted heteroaralkyloxy, $-OR^{22}$, $-N(R^{22})_2$, $-SO_2R^{21}$, $-N(R^{22})SO_2R^{21}$, $-SO_2N(R^{22})_2$, $–N(R^{22})SO_2N(R^{22})_2$, $-CON(R^{22})_2$, $-N(R^{22})CO_2R^{21}$, $-N(R^{22})CON(R^{22})_2$, $-N(R^{22})COR^{21}$, $-OC(O)N(R^{22})_2$, $-OSO_2N(R^{22})_2$, or $-N(R^{22})SO_3R^{21}$;

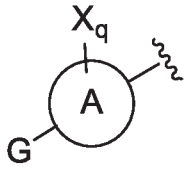
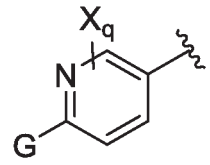
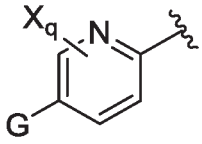
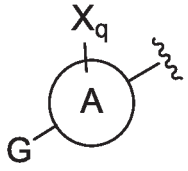
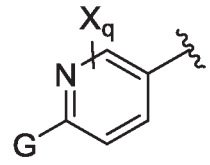
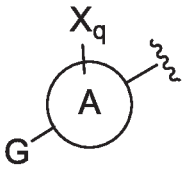
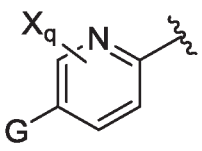
R^{17} is selected from hydrogen, halogen, -CN, optionally substituted alkyl, optionally substituted fluoroalkyl, optionally substituted alkoxy, optionally substituted cycloalkyl, optionally substituted heterocyclyl, optionally substituted cycloalkylalkyl, optionally substituted cycloalkyl-O-, optionally substituted aryl, optionally substituted aralkyl, optionally substituted heteroaryl, optionally substituted heteroaralkyl, optionally substituted aryloxy, optionally substituted aralkyloxy, optionally substituted heteroaryloxy, optionally substituted heteroaralkyloxy, $-OR^{22}$, $-N(R^{22})_2$, $-SO_2R^{21}$, $-N(R^{22})SO_2R^{21}$, $-SO_2N(R^{22})_2$, $–N(R^{22})SO_2N(R^{22})_2$, $-CON(R^{22})_2$, $-N(R^{22})CO_2R^{21}$, $-N(R^{22})CON(R^{22})_2$, $-N(R^{22})COR^{21}$, $-OC(O)N(R^{22})_2$, $-OSO_2N(R^{22})_2$, or $-N(R^{22})SO_3R^{21}$;

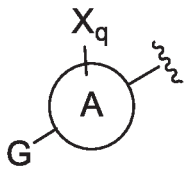
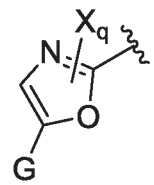
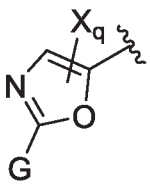
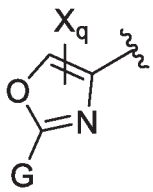
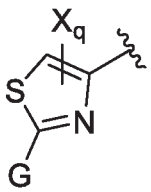
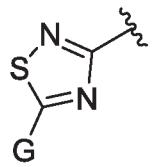
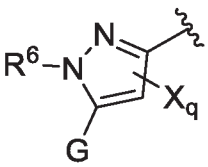
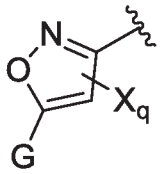
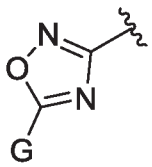
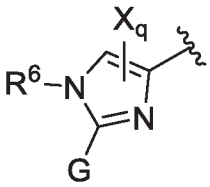
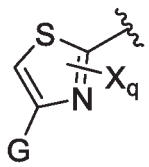
R^{18} is selected from hydrogen, halogen, -CN, optionally substituted alkyl, optionally substituted fluoroalkyl, optionally substituted alkoxy, optionally substituted cycloalkyl, optionally substituted heterocyclyl, optionally substituted cycloalkylalkyl, optionally substituted cycloalkyl-O-, optionally substituted aryl, optionally substituted aralkyl, optionally substituted heteroaryl, optionally substituted heteroaralkyl, optionally substituted aryloxy, optionally substituted aralkyloxy, optionally substituted heteroaryloxy, optionally substituted heteroaralkyloxy, $-OR^{22}$, $-N(R^{22})_2$, $-SO_2R^{21}$, $-N(R^{22})SO_2R^{21}$, $-SO_2N(R^{22})_2$, $–N(R^{22})SO_2N(R^{22})_2$,

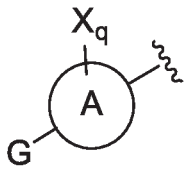
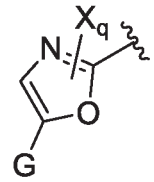
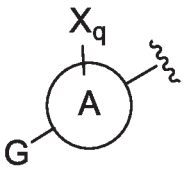
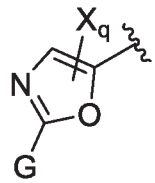
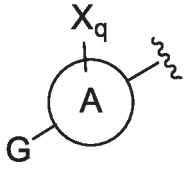
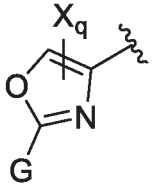
$-CON(R^{22})_2$, $-N(R^{22})CO_2R^{21}$, $-N(R^{22})CON(R^{22})_2$, $-N(R^{22})COR^{21}$, $-OC(O)N(R^{22})_2$, $-OSO_2N(R^{22})_2$, or $-N(R^{22})SO_3R^{21}$;

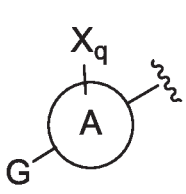
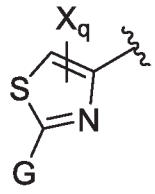
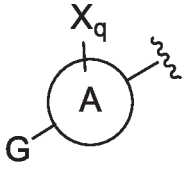
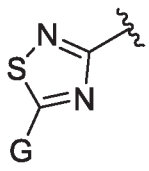
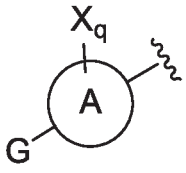
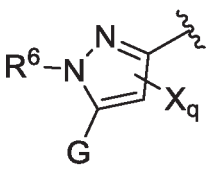
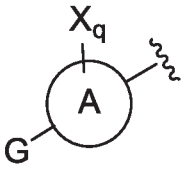
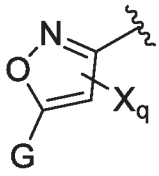
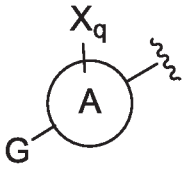
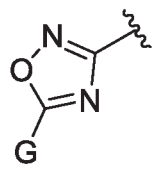
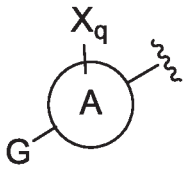
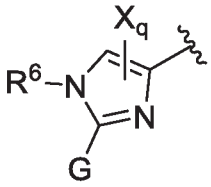
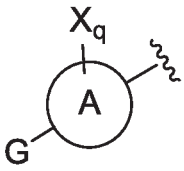
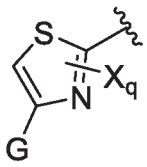
each R^{21} is independently selected from alkyl, cycloalkyl, cycloalkylalkyl, aryl, aralkyl, heterocyclyl, heterocyclylalkyl, heteroaryl, or heteroarylalkyl; and

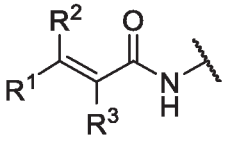
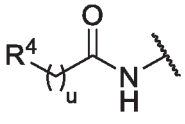
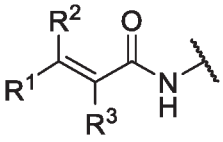
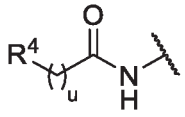
each R^{22} is independently selected from hydrogen, alkyl, cycloalkyl, cycloalkylalkyl, aryl, aralkyl, heterocyclyl, heterocyclylalkyl, heteroaryl, or heteroarylalkyl.

[00135] In some embodiments,  is  or ; and q is 0, 1, 2, or 3. In some embodiments,  is ; and q is 0, 1, 2, or 3. In some embodiments,  is ; and q is 0, 1, 2, or 3.

[00136] In some embodiments,  is , , , , , , , , , or ; R^6 is hydrogen or optionally substituted C1-C4 alkyl; and q is 0 or 1.

[00137] In some embodiments,  is . In some embodiments,  is . In some embodiments,  is . In some embodiments,



is . In some embodiments, 

is . In some embodiments, 

is . In some embodiments, 
is 
. In some embodiments, 
is 
. In some embodiments, 

is . In some embodiments, 

is .

[00138] In some embodiments, G is 
or 
. In some embodiments, G is 
. In some embodiments, G is 
.

[00139] In some embodiments, R^3 is hydrogen or –CN.

[00140] In some embodiments, L is NH.

[00141] In some embodiments, t is 2.

[00142] In some embodiments, q is 0 or 1.

[00143] In some embodiments, q is 0.

[00144] In some embodiments, X is a halogen.

[00145] In some embodiments, R^2 is hydrogen.

[00146] In some embodiments, R^3 is hydrogen.

[00147] In some embodiments, R^2 and R^3 is hydrogen.

[00148] In some embodiments, R^1 is hydrogen. In some embodiments, R^1 is optionally substituted C1-C4 alkyl. In some embodiments, R^1 is optionally substituted C1-C2 alkyl. In some embodiments, R^1 is optionally substituted C1 alkyl. In some embodiments, the C1 alkyl is substituted with an

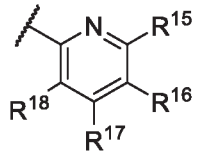
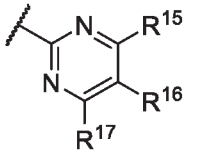
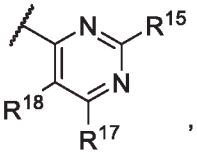
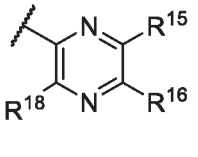
optionally substituted amino group. In some embodiments, the optionally substituted amino group is a dimethylamino.

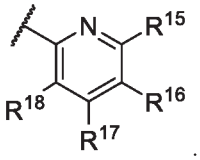
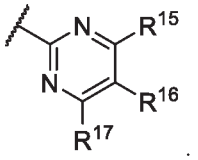
[00149] In some embodiments, R^1 is $–CH_2$-$N(Me)_2$.

[00150] In some embodiments, R^1 is optionally substituted heterocyclylalkyl. In some embodiments, the optionally substituted heterocyclylalkyl comprises an optionally substituted C1 alkyl. In some embodiments, the optionally substituted heterocyclylalkyl comprises an optionally substituted N-linked heterocyclyl. In some embodiments, the optionally substituted N-linked heterocyclyl is an N-linked pyrrolidine or piperidine.

[00151] In some embodiments, n is 1 and m is 1. In some embodiments, n is 1 and m is 2. In some embodiments, n is 1 and m is 3.

[00152] In some embodiments, Y is selected from:




or

.

[00153] In some embodiments, Y is:

. In some embodiments, Y is:

.

[00154] In some embodiments, R^{15} is selected from hydrogen, halogen, -CN, and optionally substituted alkyl. In some embodiments, R^{15} is hydrogen.

[00155] In some embodiments, R^{16} is selected from hydrogen, halogen, -CN, optionally substituted alkyl, optionally substituted fluoroalkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted alkoxy, optionally substituted cycloalkyl, optionally substituted heterocyclyl, optionally substituted cycloalkylalkyl, optionally substituted cycloalkyl-O-, optionally substituted aryl, optionally substituted aralkyl, optionally substituted heteroaryl, optionally substituted heteroaralkyl, optionally substituted aryloxy, optionally substituted aralkyloxy, optionally substituted heteroaryloxy, optionally substituted heteroaralkyloxy, $-OR^{22}$, $-N(R^{22})_2$, $-SO_2R^{21}$, $-N(R^{22})SO_2R^{21}$, $-SO_2N(R^{22})_2$, $–N(R^{22})SO_2N(R^{22})_2$, $-CON(R^{22})_2$, $-N(R^{22})CO_2R^{21}$, $-N(R^{22})CON(R^{22})_2$, $-N(R^{22})COR^{21}$, $-OC(O)N(R^{22})_2$, $-OSO_2N(R^{22})_2$, or $-N(R^{22})SO_3R^{21}$.

[00156] In some embodiments, R^{16} is selected from optionally substituted alkenyl, optionally substituted alkynyl. In some embodiments, R^{16} is selected from optionally substituted alkynyl.

[00157] In some embodiments, R^{16} is selected from hydrogen, halogen, -CN, and optionally substituted alkyl. In some embodiments, R^{16} is hydrogen.

[00158] In some embodiments, R^{17} is selected from hydrogen, halogen, -CN, and optionally substituted alkyl. In some embodiments, R^{17} is hydrogen.

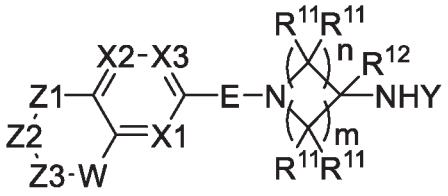
[00159] In some embodiments, R^{18} is selected from hydrogen, halogen, -CN, and optionally substituted alkyl. In some embodiments, R^{18} is hydrogen.

[00160] In some embodiments, R^{15} and R^{16} are hydrogen. In some embodiments, R^{17} and R^{18} are hydrogen.

[00161] In some embodiments, E is a bond. In some embodiments, E is $-SO_2-$. In some embodiments, E is -C(O)-. In some embodiments, E is $–CH_2-$. In some embodiments, E is $-CH(R^4)-$. In some embodiments, E is $-C(R^4)_2-$.

[00162] In some embodiments, the heteroaromatic CDK inhibitory compound of Formula (I) or Formula (II) described herein has a structure provided in Table 1.

[00163] One embodiment provides a compound, or pharmaceutically acceptable salt or solvate thereof, having the structure of Formula (III):



(III)

wherein,

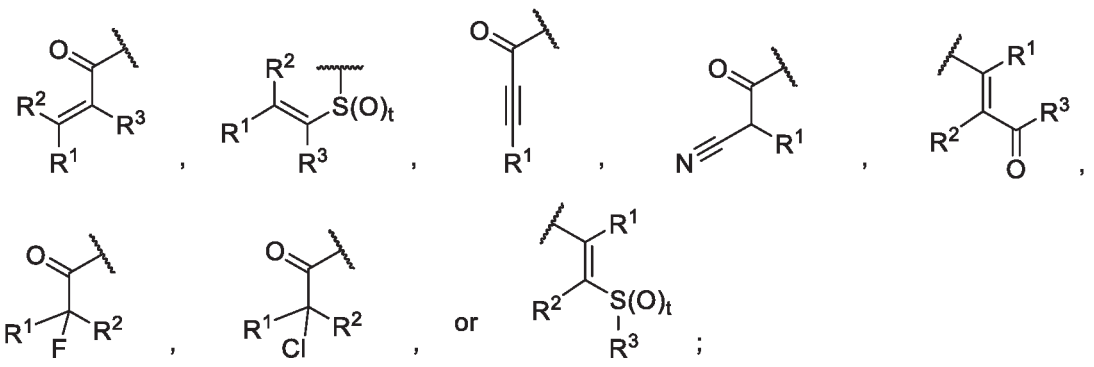
Z1, Z2, and Z3 are selected from CH_2 or N-G, with the provision that only one of Z1, Z2, or Z3 is N-G;

X1, X2 and X3 are each independently N or C-R^7;

W is absent, O, S, SO_2, NH, NR^{12}, $C(R^{11})_2$;

E is selected from a bond, $-SO_2-$, -C(O)-, $–CH_2-$, $-CH(R^4)-$, or $-C(R^4)_2-$;

G is selected from a group having the structure:



wherein,

t is 0, 1, or 2;

R^1 is selected from hydrogen, optionally substituted C1-C4 alkyl, or optionally substituted heterocyclylalkyl;

R^2 is selected from hydrogen, or optionally substituted C1-C4 alkyl;

R^3 is selected from hydrogen, -CN, or optionally substituted C1-C4 alkyl;

each R^4 is independently selected from optionally substituted C1-C4 alkyl, or optionally substituted heterocyclylalkyl;

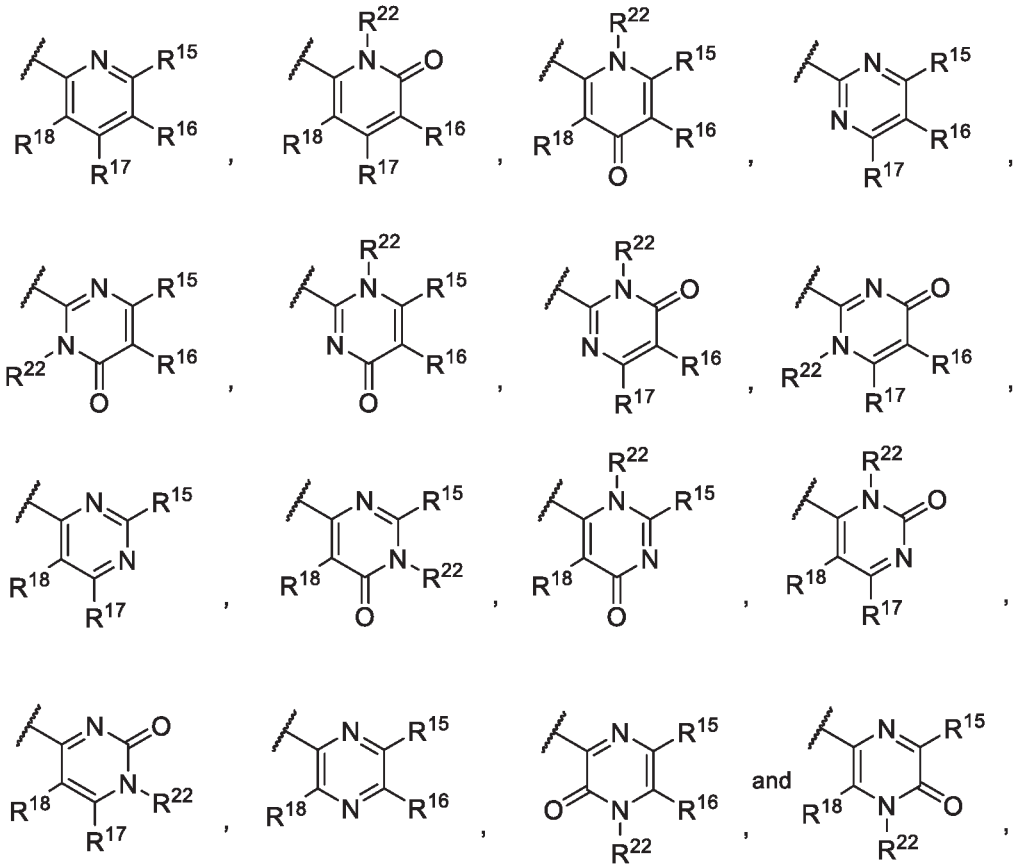
each R^7 is independently hydrogen, halogen, optionally substituted C1-C4 alkyl, optionally substituted C1-C4 alkoxy, optionally substituted cycloalkyl, optionally substituted heterocyclyl, optionally substituted aryl, or optionally substituted heteroaryl

each R^{11} is independently hydrogen, halogen, optionally substituted C1-C6 alkyl, or two R^{11} groups on the same carbon atom form an oxo;

each R^{12} is independently hydrogen or optionally substituted C1-C4 alkyl;

n is 0, 1, 2, or 3; m is 0, 1, 2, or 3;

Y is a group selected from:



wherein,

R^{15} is selected from hydrogen, halogen, -CN, optionally substituted alkyl, optionally substituted alkoxy, optionally substituted cycloalkyl, optionally substituted heterocyclyl, optionally substituted cycloalkylalkyl, optionally substituted cycloalkyl-O-, optionally substituted aryl, optionally substituted aralkyl, optionally substituted heteroaryl, optionally substituted heteroaralkyl, optionally substituted aryloxy, optionally substituted aralkyloxy, optionally

substituted heteroaryloxy, optionally substituted heteroaralkyloxy, -$N(R^{22})_2$, -SO_2R^{21}, -$N(R^{22})SO_2R^{21}$, -$SO_2N(R^{22})_2$, –$N(R^{22})SO_2N(R^{22})_2$, -$CON(R^{22})_2$, -$N(R^{22})CO_2R^{21}$, -$N(R^{22})CON(R^{22})_2$, -$N(R^{22})COR^{21}$, -$OC(O)N(R^{22})_2$, -$OSO_2N(R^{22})_2$, or -$N(R^{22})SO_3R^{21}$;

R^{16} is selected from hydrogen, halogen, -CN, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted alkoxy, optionally substituted cycloalkyl, optionally substituted heterocyclyl, optionally substituted cycloalkylalkyl, optionally substituted cycloalkyl-O-, optionally substituted aryl, optionally substituted aralkyl, optionally substituted heteroaryl, optionally substituted heteroaralkyl, optionally substituted aryloxy, optionally substituted aralkyloxy, optionally substituted heteroaryloxy, optionally substituted heteroaralkyloxy, -$N(R^{22})_2$, -SO_2R^{21}, -$N(R^{22})SO_2R^{21}$, -$SO_2N(R^{22})_2$, –$N(R^{22})SO_2N(R^{22})_2$, -$CON(R^{22})_2$, -$N(R^{22})CO_2R^{21}$, -$N(R^{22})CON(R^{22})_2$, -$N(R^{22})COR^{21}$, -$OC(O)N(R^{22})_2$, -$OSO_2N(R^{22})_2$, or -$N(R^{22})SO_3R^{21}$;

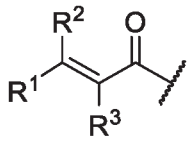
R^{17} is selected from hydrogen, halogen, -CN, optionally substituted alkyl, optionally substituted alkoxy, optionally substituted cycloalkyl, optionally substituted heterocyclyl, optionally substituted cycloalkylalkyl, optionally substituted cycloalkyl-O-, optionally substituted aryl, optionally substituted aralkyl, optionally substituted heteroaryl, optionally substituted heteroaralkyl, optionally substituted aryloxy, optionally substituted aralkyloxy, optionally substituted heteroaryloxy, optionally substituted heteroaralkyloxy, -$N(R^{22})_2$, -SO_2R^{21}, -$N(R^{22})SO_2R^{21}$, -$SO_2N(R^{22})_2$, –$N(R^{22})SO_2N(R^{22})_2$, -$CON(R^{22})_2$, -$N(R^{22})CO_2R^{21}$, -$N(R^{22})CON(R^{22})_2$, -$N(R^{22})COR^{21}$, -$OC(O)N(R^{22})_2$, -$OSO_2N(R^{22})_2$, or -$N(R^{22})SO_3R^{21}$;

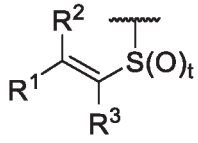
R^{18} is selected from hydrogen, halogen, -CN, optionally substituted alkyl, optionally substituted alkoxy, optionally substituted cycloalkyl, optionally substituted heterocyclyl, optionally substituted cycloalkylalkyl, optionally substituted cycloalkyl-O-, optionally substituted aryl, optionally substituted aralkyl, optionally substituted heteroaryl, optionally substituted heteroaralkyl, optionally substituted aryloxy, optionally substituted aralkyloxy, optionally substituted heteroaryloxy, optionally substituted heteroaralkyloxy, -$N(R^{22})_2$, -SO_2R^{21}, -$N(R^{22})SO_2R^{21}$, -$SO_2N(R^{22})_2$, –$N(R^{22})SO_2N(R^{22})_2$, -$CON(R^{22})_2$, -$N(R^{22})CO_2R^{21}$, -$N(R^{22})CON(R^{22})_2$, -$N(R^{22})COR^{21}$, -$OC(O)N(R^{22})_2$, -$OSO_2N(R^{22})_2$, or -$N(R^{22})SO_3R^{21}$;

each R^{21} is independently selected from alkyl, cycloalkyl, cycloalkylalkyl, aryl, aralkyl, heterocyclyl, heterocyclylalkyl, heteroaryl, or heteroarylalkyl; and

each R^{22} is independently selected from hydrogen, alkyl, cycloalkyl, cycloalkylalkyl, aryl, aralkyl, heterocyclyl, heterocyclylalkyl, heteroaryl, or heteroarylalkyl.

[00164] In some embodiments, Z1 is N-G.

[00165] In some embodiments, G is .

[00166] In some embodiments, G is .

[00167] In some embodiments, R^3 is hydrogen or –CN.

[00168] In some embodiments, t is 2.

[00169] In some embodiments, W is O. In some embodiments, W is $–CH_2-$. In some embodiments, W is NH or NR^{12}. In some embodiments, W is SO_2. In some embodiments, W is absent.

[00170] In some embodiments, R^2 is hydrogen.

[00171] In some embodiments, R^3 is hydrogen.

[00172] In some embodiments, R^2 and R^3 is hydrogen.

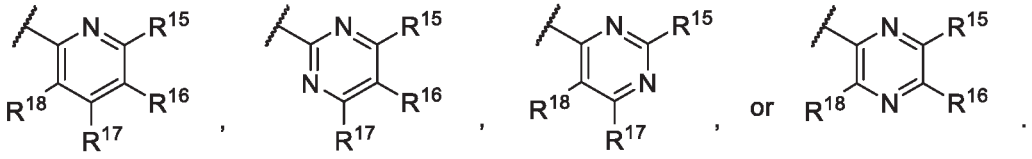
[00173] In some embodiments, R^1 is hydrogen. In some embodiments, R^1 is optionally substituted C1-C4 alkyl. In some embodiments, R^1 is optionally substituted C1-C2 alkyl. In some embodiments, R^1 is optionally substituted C1 alkyl. In some embodiments, the C1 alkyl is substituted with an optionally substituted amino group. In some embodiments, the optionally substituted amino group is a dimethylamino.

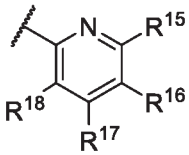
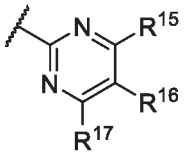
[00174] In some embodiments, R^1 is $–CH_2-N(Me)_2$.

[00175] In some embodiments, R^1 is optionally substituted heterocyclylalkyl. In some embodiments, the optionally substituted heterocyclylalkyl comprises an optionally substituted C1 alkyl. In some embodiments, the optionally substituted heterocyclylalkyl comprises an optionally substituted N-linked heterocyclyl. In some embodiments, the optionally substituted N-linked heterocyclyl is an N-linked pyrrolidine or piperidine.

[00176] In some embodiments, n is 1 and m is 1. In some embodiments, n is 1 and m is 2. In some embodiments, n is 1 and m is 3.

[00177] In some embodiments, Y is selected from:



[00178] In some embodiments, Y is: . In some embodiments, Y is: .

[00179] In some embodiments, R^{15} is selected from hydrogen, halogen, -CN, and optionally substituted alkyl. In some embodiments, R^{15} is hydrogen.

[00180] In some embodiments, R^{16} is selected from hydrogen, halogen, -CN, optionally substituted alkyl, optionally substituted alkoxy, optionally substituted cycloalkyl, optionally substituted heterocyclyl, optionally substituted cycloalkylalkyl, optionally substituted cycloalkyl-O-, optionally substituted aryl, optionally substituted aralkyl, optionally substituted heteroaryl, optionally substituted heteroaralkyl, optionally substituted aryloxy, optionally substituted aralkyloxy, optionally substituted heteroaryloxy, optionally substituted heteroaralkyloxy, $-N(R^{22})_2$, $-SO_2R^{21}$, $-N(R^{22})SO_2R^{21}$, $-SO_2N(R^{22})_2$, $-N(R^{22})SO_2N(R^{22})_2$, $-CON(R^{22})_2$, $-N(R^{22})CO_2R^{21}$, $-N(R^{22})CON(R^{22})_2$, $-N(R^{22})COR^{21}$, $-OC(O)N(R^{22})_2$, $-OSO_2N(R^{22})_2$, or $-N(R^{22})SO_3R^{21}$.

[00181] In some embodiments, R^{16} is selected from optionally substituted alkenyl, optionally substituted alkynyl. In some embodiments, R^{16} is selected from optionally substituted alkynyl.

[00182] In some embodiments, R^{16} is selected from hydrogen, halogen, -CN, and optionally substituted alkyl. In some embodiments, R^{16} is hydrogen.

[00183] In some embodiments, R^{17} is selected from hydrogen, halogen, -CN, and optionally substituted alkyl. In some embodiments, R^{17} is hydrogen.

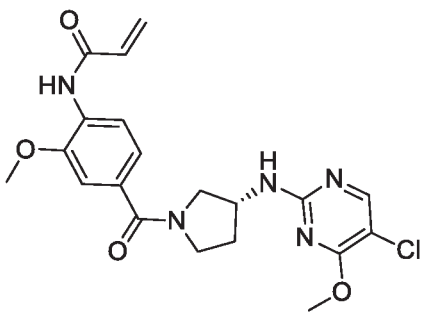
[00184] In some embodiments, R^{18} is selected from hydrogen, halogen, -CN, and optionally substituted alkyl. In some embodiments, R^{18} is hydrogen.

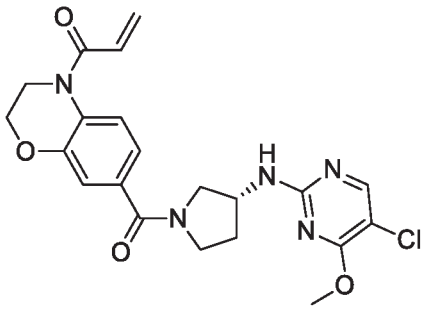
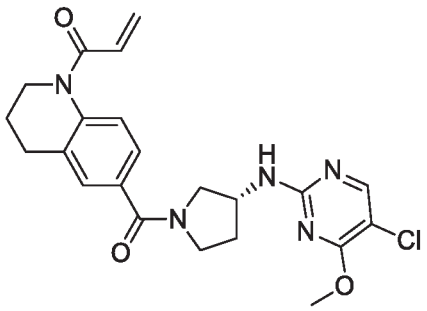
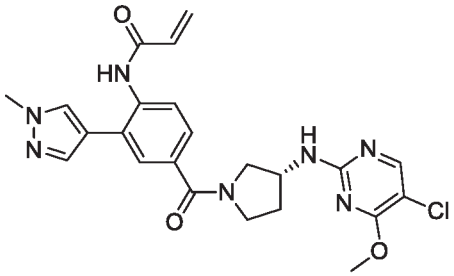
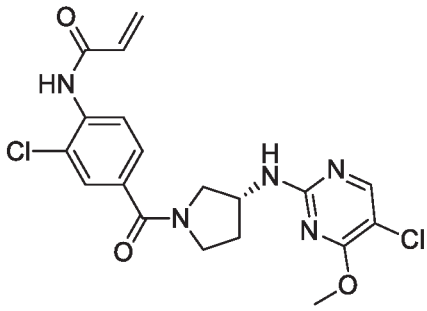
[00185] In some embodiments, R^{15} and R^{16} are hydrogen. In some embodiments, R^{17} and R^{18} are hydrogen.

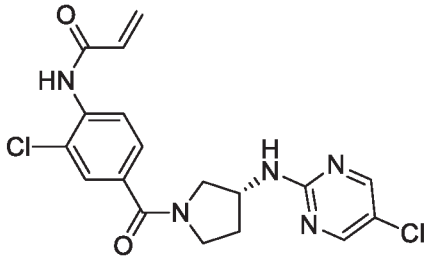
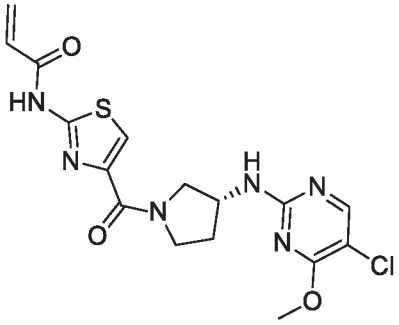
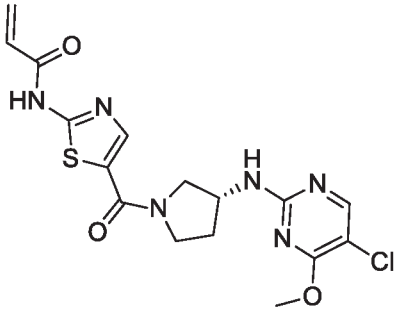
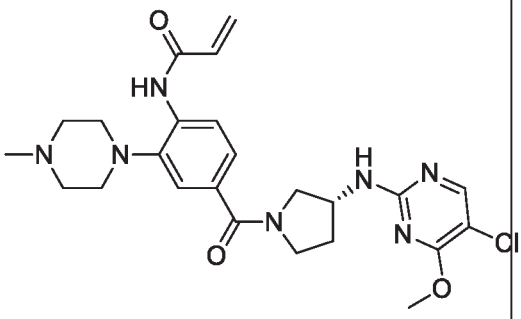
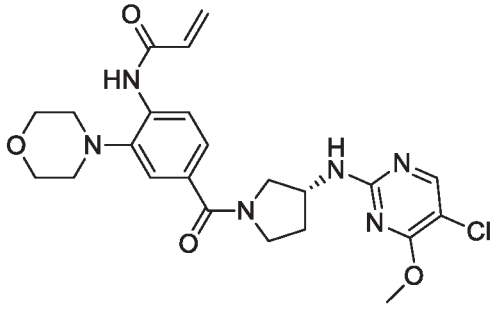
[00186] In some embodiments, E is a bond. In some embodiments, E is $-SO_2-$. In some embodiments, E is -C(O)-. In some embodiments, E is $-CH_2-$. In some embodiments, E is $-CH(R^4)-$. In some embodiments, E is $-C(R^4)_2-$.

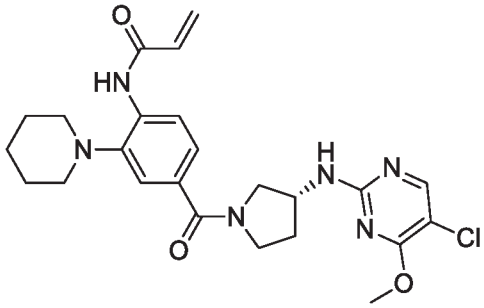
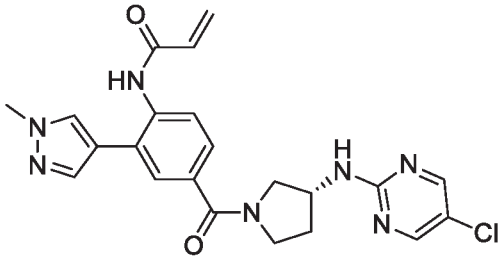
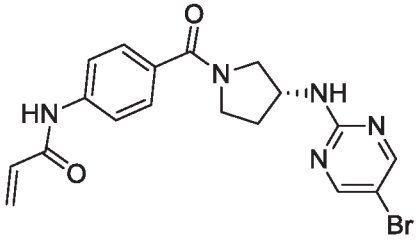
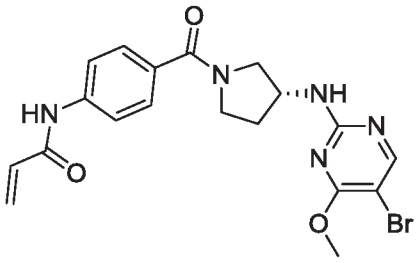
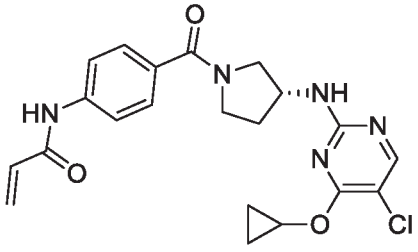
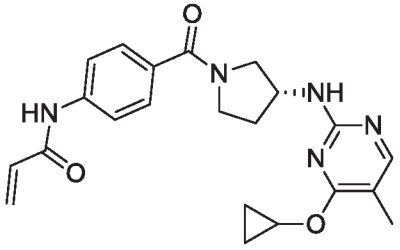
[00187] In some embodiments, the heteroaromatic CDK inhibitory compound of Formula (III) described herein has a structure provided in Table 1.

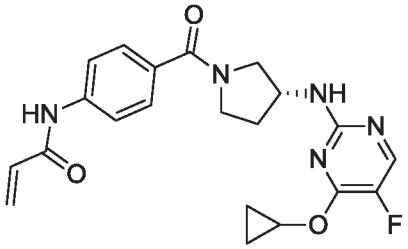
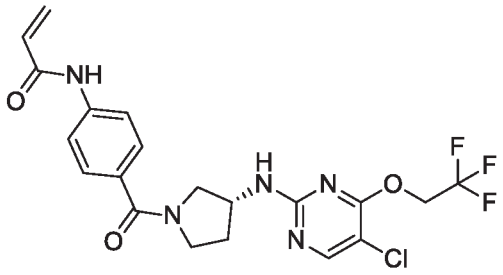
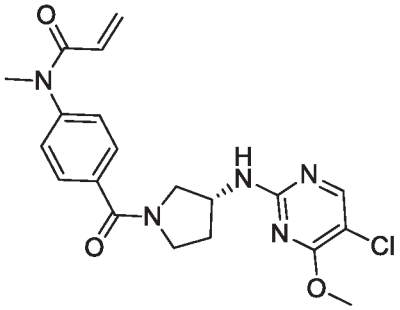
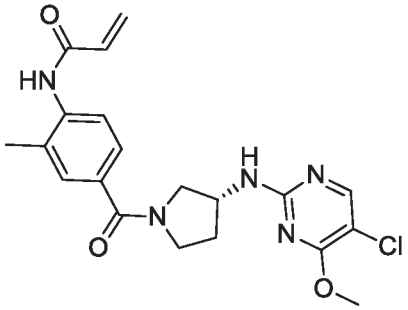
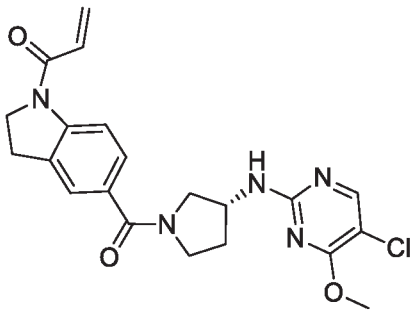
Table 1

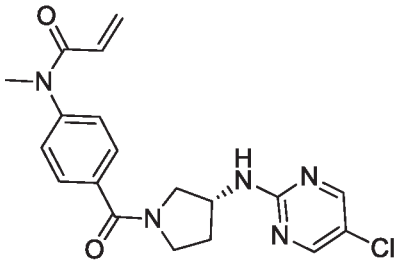
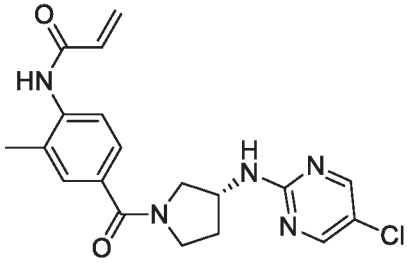
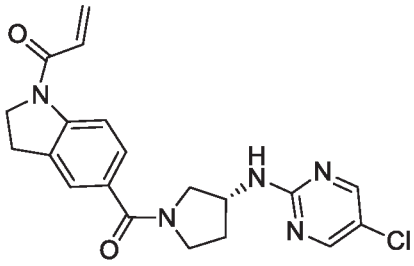
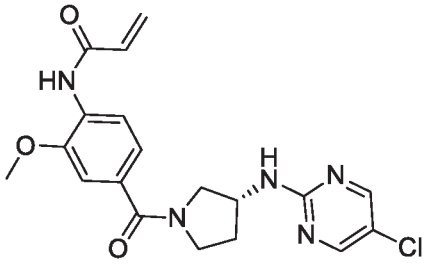
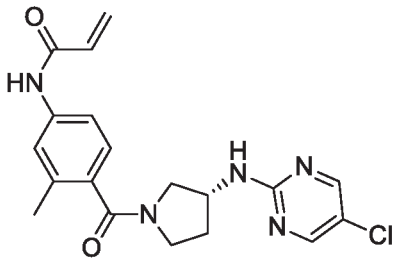
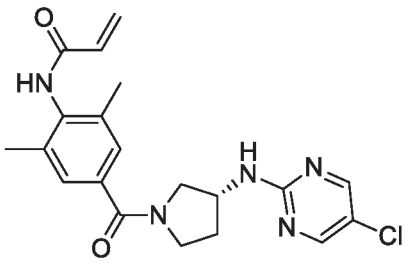
Synthetic Chemistry Example	Compound Structure	Compound Name
1		(R)-N-(4-(3-((5-chloro-4-methoxypyrimidin-2-yl)amino)pyrrolidine-1-carbonyl)-2-methoxyphenyl)acrylamide

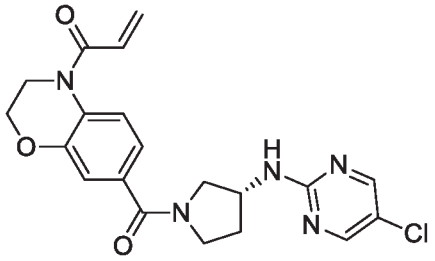
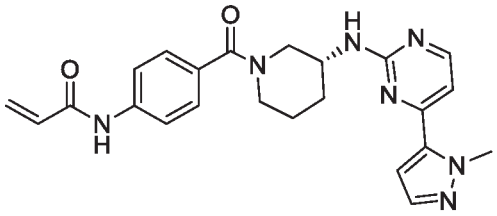
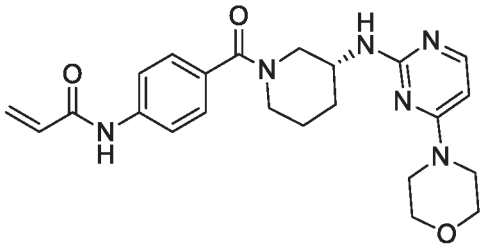
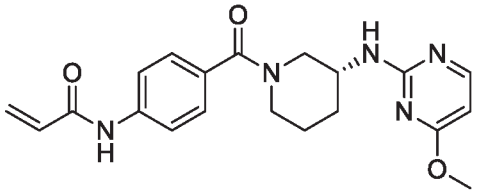
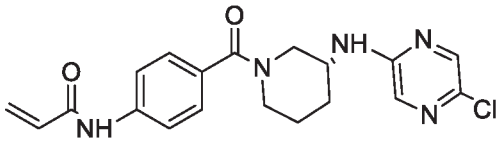
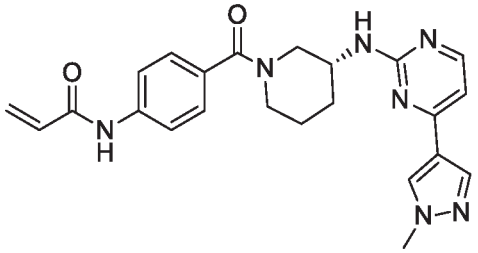
Synthetic Chemistry Example	Compound Structure	Compound Name
2		(R)-1-(7-(3-((5-chloro-4-methoxypyrimidin-2-yl)amino)pyrrolidine-1-carbonyl)-2H-benzo[b][1,4]oxazin-4(3H)-yl)prop-2-en-1-one
3		(R)-1-(6-(3-((5-chloro-4-methoxypyrimidin-2-yl)amino)pyrrolidine-1-carbonyl)-3,4-dihydroquinolin-1(2H)-yl)prop-2-en-1-one
4		(R)-N-(4-(3-((5-chloro-4-methoxypyrimidin-2-yl)amino)pyrrolidine-1-carbonyl)-2-(1-methyl-1H-pyrazol-4-yl)phenyl)acrylamide
5		(R)-N-(2-chloro-4-(3-((5-chloro-4-methoxypyrimidin-2-yl)amino)pyrrolidine-1-carbonyl)phenyl)acrylamide

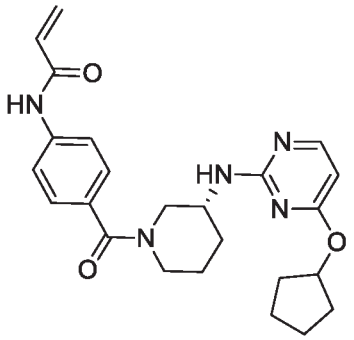
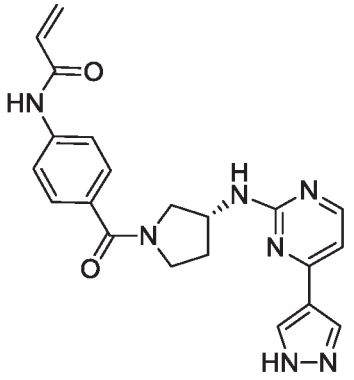
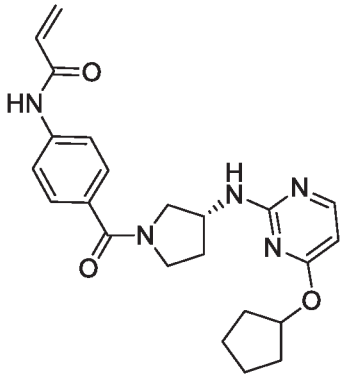
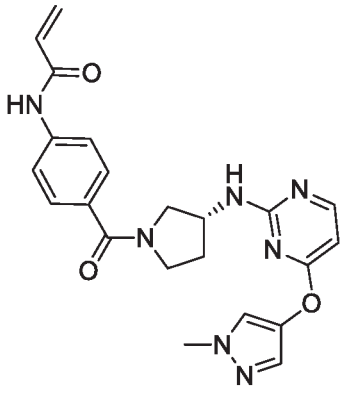
Synthetic Chemistry Example	Compound Structure	Compound Name
6		(R)-N-(2-chloro-4-(3-((5-chloropyrimidin-2-yl)amino)pyrrolidine-1-carbonyl)phenyl)acrylamide
7		(R)-N-(4-(3-((5-chloro-4-methoxypyrimidin-2-yl)amino)pyrrolidine-1-carbonyl)thiazol-2-yl)acrylamide
8		(R)-N-(4-(3-((5-chloro-4-methoxypyrimidin-2-yl)amino)pyrrolidine-1-carbonyl)-2-(4-methylpiperazin-1-yl)phenyl)acrylamide
9		(R)-N-(4-(3-((5-chloro-4-methoxypyrimidin-2-yl)amino)pyrrolidine-1-carbonyl)-2-(4-methylpiperazin-1-yl)phenyl)acrylamide
10		(R)-N-(4-(3-((5-chloro-4-methoxypyrimidin-2-yl)amino)pyrrolidine-1-carbonyl)-2-morpholinophenyl)acrylamide

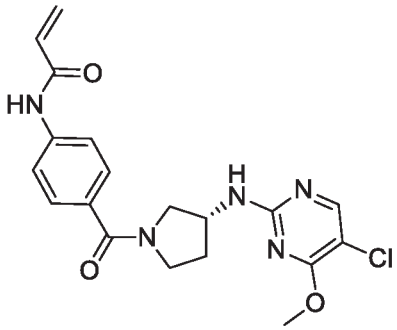
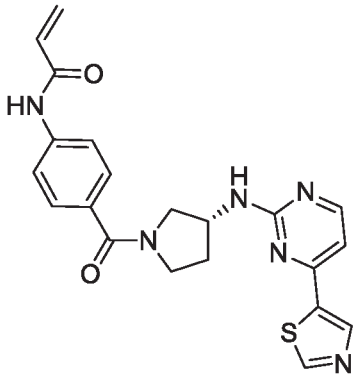
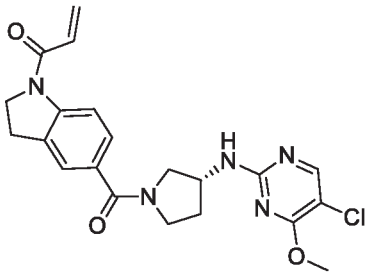
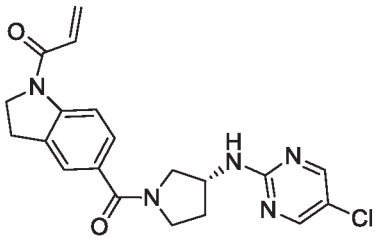
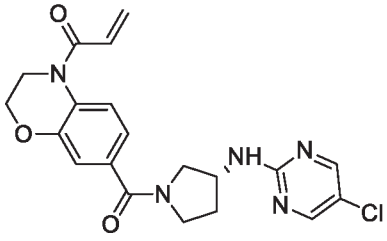
Synthetic Chemistry Example	Compound Structure	Compound Name
11		(R)-N-(4-(3-((5-chloro-4-methoxypyrimidin-2-yl)amino)pyrrolidine-1-carbonyl)-2-(piperidin-1-yl)phenyl)acrylamide
12		(R)-N-(4-(3-((5-chloropyrimidin-2-yl)amino)pyrrolidine-1-carbonyl)-2-(1-methyl-1H-pyrazol-4-yl)phenyl)acrylamide
19		(R)-N-(4-(3-((5-bromopyrimidin-2-yl)amino)pyrrolidine-1-carbonyl)phenyl)acrylamide
20		(R)-N-(4-(3-((5-bromo-4-methoxypyrimidin-2-yl)amino)pyrrolidine-1-carbonyl)phenyl)acrylamide
21		(R)-N-(4-(3-((5-chloro-4-cyclopropoxypyrimidin-2-yl)amino)pyrrolidine-1-carbonyl)phenyl)acrylamide
22		(R)-N-(4-(3-((4-cyclopropoxy-5-methylpyrimidin-2-yl)amino)pyrrolidine-1-carbonyl)phenyl)acrylamide

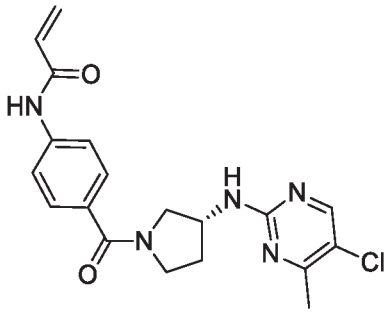
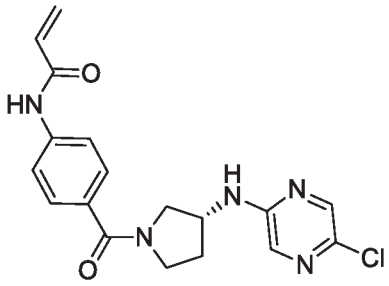
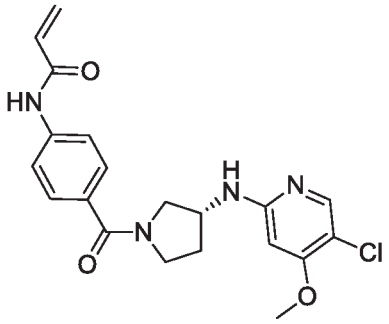
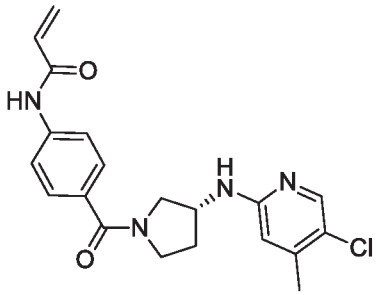
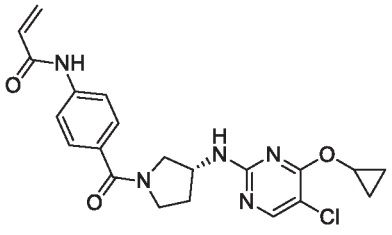
Synthetic Chemistry Example	Compound Structure	Compound Name
23		(R)-N-(4-(3-((4-cyclopropoxy-5-fluoropyrimidin-2-yl)amino)pyrrolidine-1-carbonyl)phenyl)acrylamide
24		(R)-N-(4-(3-((5-chloro-4-(2,2,2-trifluoroethoxy)pyrimidin-2-yl)amino)pyrrolidine-1-carbonyl)phenyl)acrylamide
25		(R)-N-(4-(3-((5-chloro-4-methoxypyrimidin-2-yl)amino)pyrrolidine-1-carbonyl)phenyl)-N-methylacrylamide
26		(R)-N-(4-(3-((5-chloro-4-methoxypyrimidin-2-yl)amino)pyrrolidine-1-carbonyl)-2-methylphenyl)acrylamide
27		(R)-1-(5-(3-((5-chloro-4-methoxypyrimidin-2-yl)amino)pyrrolidine-1-carbonyl)indolin-1-yl)prop-2-en-1-one

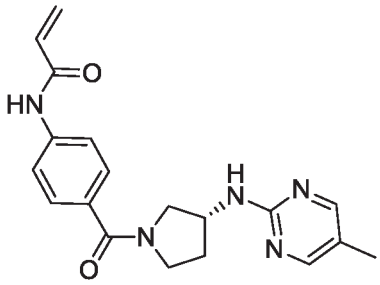
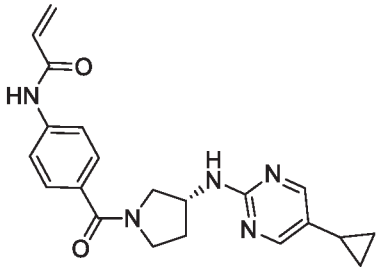
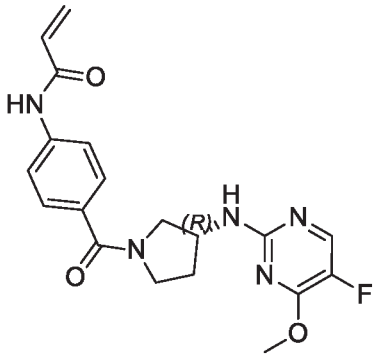
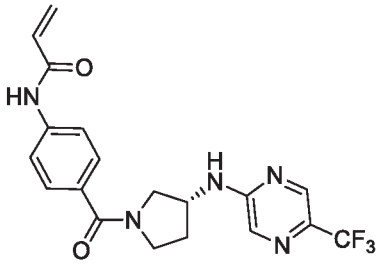
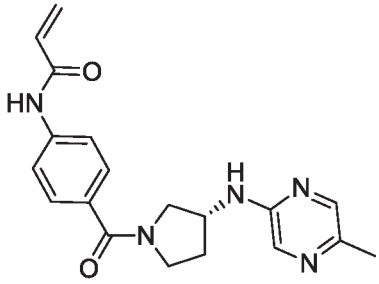
Synthetic Chemistry Example	Compound Structure	Compound Name
28		(R)-N-(4-(3-((5-chloropyrimidin-2-yl)amino)pyrrolidine-1-carbonyl)phenyl)-N-methylacrylamide
29		(R)-N-(4-(3-((5-chloropyrimidin-2-yl)amino)pyrrolidine-1-carbonyl)-2-methylphenyl)acrylamide
30		(R)-1-(5-(3-((5-chloropyrimidin-2-yl)amino)pyrrolidine-1-carbonyl)indolin-1-yl)prop-2-en-1-one
31		(R)-N-(4-(3-((5-chloropyrimidin-2-yl)amino)pyrrolidine-1-carbonyl)-2-methoxyphenyl)acrylamide
32		(R)-N-(4-(3-((5-chloropyrimidin-2-yl)amino)pyrrolidine-1-carbonyl)-3-methylphenyl)acrylamide
33		(R)-N-(4-(3-((5-chloropyrimidin-2-yl)amino)pyrrolidine-1-carbonyl)-2,6-dimethylphenyl)acrylamide

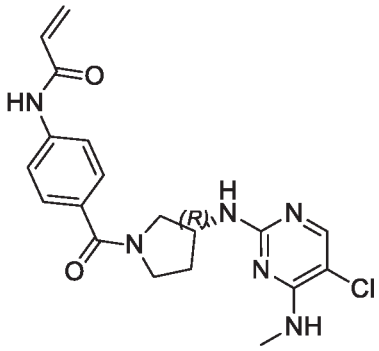
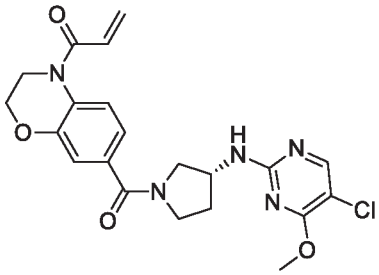
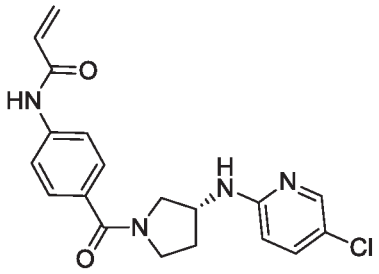
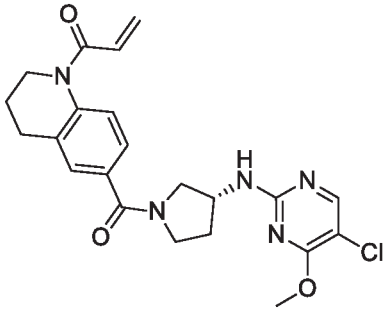
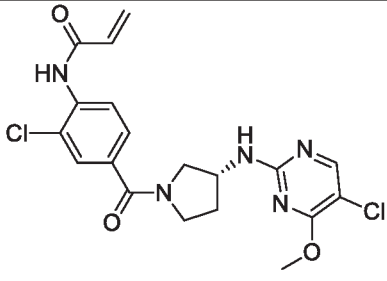
Synthetic Chemistry Example	Compound Structure	Compound Name
34		(R)-1-(7-(3-((5-chloropyrimidin-2-yl)amino)pyrrolidine-1-carbonyl)-2H-benzo[b][1,4]oxazin-4(3H)-yl)prop-2-en-1-one
35		(R)-N-(4-(3-((4-(1-methyl-1H-pyrazol-5-yl)pyrimidin-2-yl)amino)piperidine-1-carbonyl)phenyl)acrylamide
36		(R)-N-(4-(3-((4-morpholinopyrimidin-2-yl)amino)piperidine-1-carbonyl)phenyl)acrylamide
37		(R)-N-(4-(3-((4-methoxypyrimidin-2-yl)amino)piperidine-1-carbonyl)phenyl)acrylamide
38		(R)-N-(4-(3-((5-chloropyrazin-2-yl)amino)piperidine-1-carbonyl)phenyl)acrylamide
39		(R)-N-(4-(3-((4-(1-methyl-1H-pyrazol-4-yl)pyrimidin-2-yl)amino)piperidine-1-carbonyl)phenyl)acrylamide

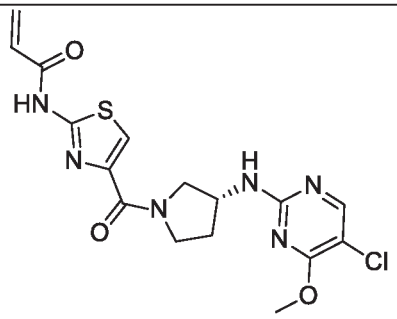
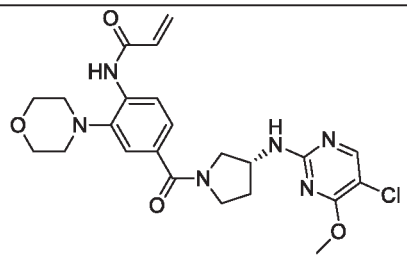
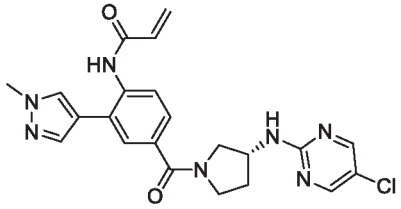
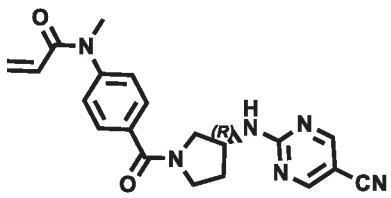
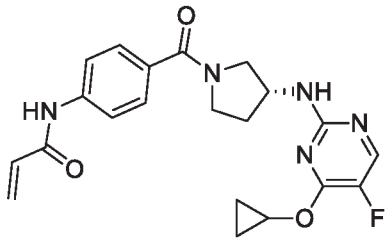
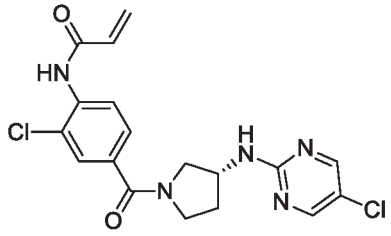
Synthetic Chemistry Example	Compound Structure	Compound Name
40		(R)-N-(4-(3-((4-(cyclopentyloxy)pyrimidin-2-yl)amino)piperidine-1-carbonyl)phenyl)acrylamide
44		(R)-N-(4-(3-((4-(1H-pyrazol-4-yl)pyrimidin-2-yl)amino)pyrrolidine-1-carbonyl)phenyl)acrylamide
45		(R)-N-(4-(3-((4-(cyclopentyloxy)pyrimidin-2-yl)amino)pyrrolidine-1-carbonyl)phenyl)acrylamide
46		(R)-N-(4-(3-((4-((1-methyl-1H-pyrazol-4-yl)oxy)pyrimidin-2-yl)amino)pyrrolidine-1-carbonyl)phenyl)acrylamide

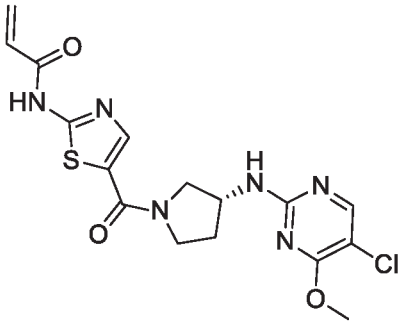
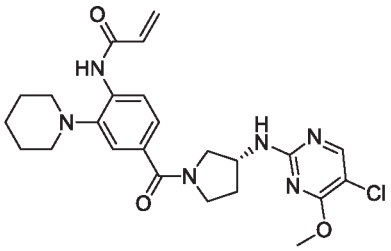
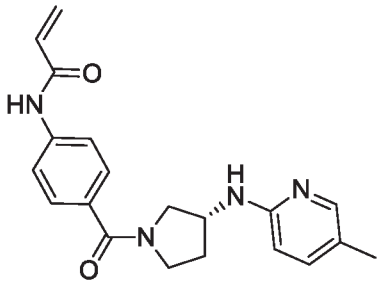
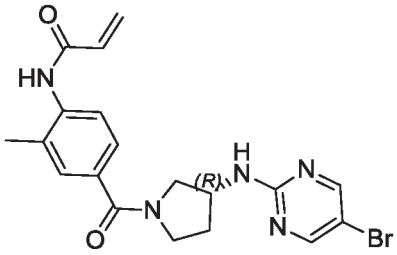
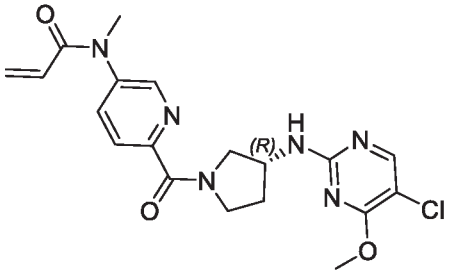
Synthetic Chemistry Example	Compound Structure	Compound Name
47		(R)-N-(4-(3-((5-chloro-4-methoxypyrimidin-2-yl)amino)pyrrolidine-1-carbonyl)phenyl)acrylamide
48		(R)-N-(4-(3-((4-(thiazol-5-yl)pyrimidin-2-yl)amino)pyrrolidine-1-carbonyl)phenyl)acrylamide
49		(R)-1-(5-(3-((5-chloro-4-methoxypyrimidin-2-yl)amino)pyrrolidine-1-carbonyl)indolin-1-yl)prop-2-en-1-one
50		(R)-1-(5-(3-((5-chloropyrimidin-2-yl)amino)pyrrolidine-1-carbonyl)indolin-1-yl)prop-2-en-1-one
51		(R)-1-(7-(3-((5-chloropyrimidin-2-yl)amino)pyrrolidine-1-carbonyl)-2H-benzo[b][1,4]oxazin-4(3H)-yl)prop-2-en-1-one

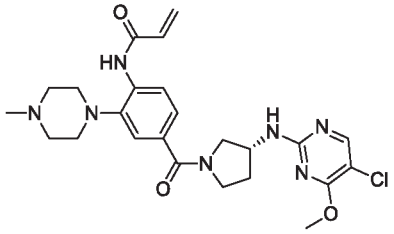
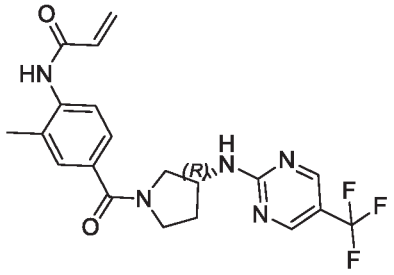
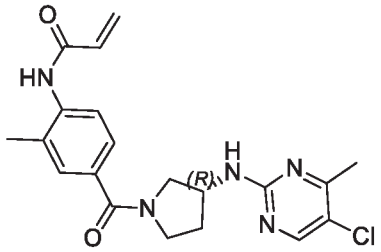
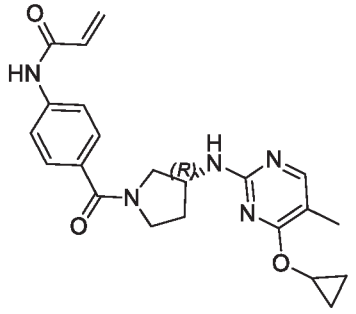
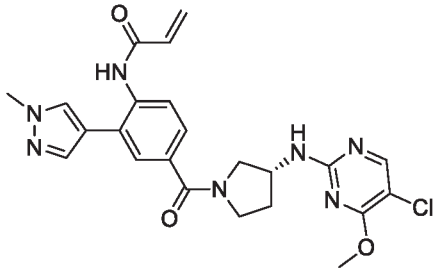
Synthetic Chemistry Example	Compound Structure	Compound Name
52		(*R*)-*N*-(4-(3-((5-chloro-4-methylpyrimidin-2-yl)amino)pyrrolidine-1-carbonyl)phenyl)acrylamide
53		(*R*)-*N*-(4-(3-((5-chloropyrazin-2-yl)amino)pyrrolidine-1-carbonyl)phenyl)acrylamide
54		(*R*)-*N*-(4-(3-((5-chloro-4-methoxypyridin-2-yl)amino)pyrrolidine-1-carbonyl)phenyl)acrylamide
55		(*R*)-*N*-(4-(3-((5-chloro-4-methylpyridin-2-yl)amino)pyrrolidine-1-carbonyl)phenyl)acrylamide
56		(*R*)-*N*-(4-(3-((5-chloro-4-cyclopropoxypyrimidin-2-yl)amino)pyrrolidine-1-carbonyl)phenyl)acrylamide

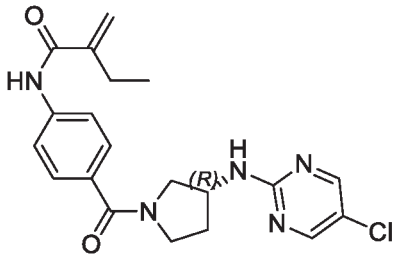
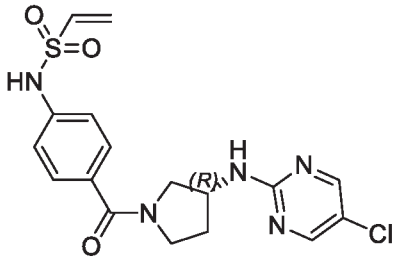
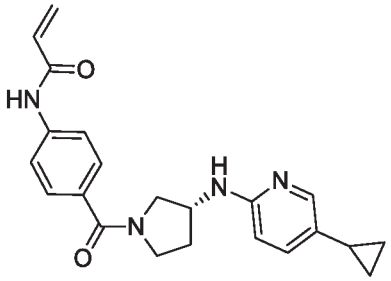
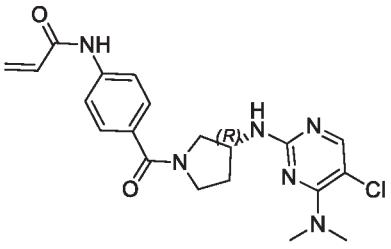
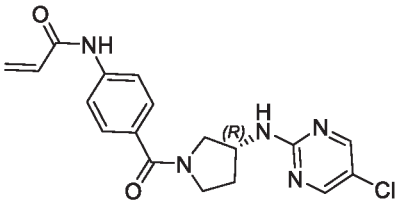
Synthetic Chemistry Example	Compound Structure	Compound Name
57		(R)-N-(4-(3-((5-methylpyrimidin-2-yl)amino)pyrrolidine-1-carbonyl)phenyl)acrylamide
58		(*R*)-*N*-(4-(3-((5-cyclopropylpyrimidin-2-yl)amino)pyrrolidine-1-carbonyl)phenyl)acrylamide
59		(*R*)-*N*-(4-(3-((5-fluoro-4-methoxypyrimidin-2-yl)amino)pyrrolidine-1-carbonyl)phenyl)acrylamide
60		(*R*)-*N*-(4-(3-((5-(trifluoromethyl)pyrazin-2-yl)amino)pyrrolidine-1-carbonyl)phenyl)acrylamide
61		(*R*)-*N*-(4-(3-((5-methylpyrazin-2-yl)amino)pyrrolidine-1-carbonyl)phenyl)acrylamide

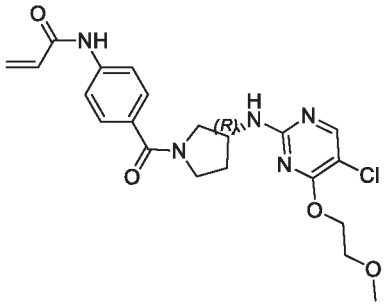
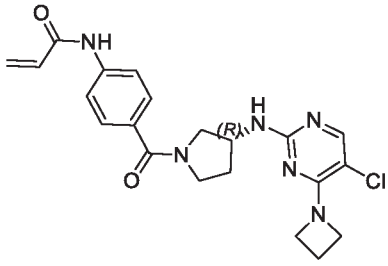
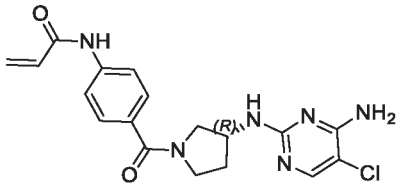
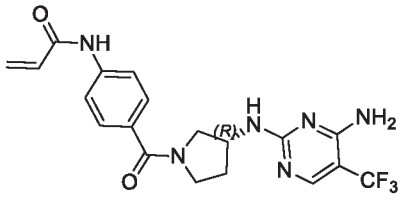
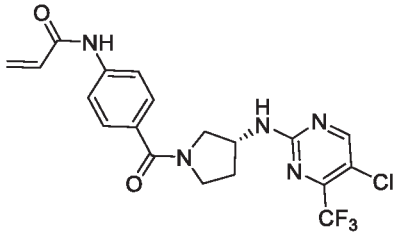
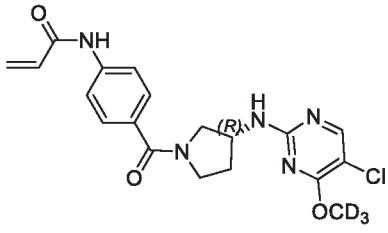
Synthetic Chemistry Example	Compound Structure	Compound Name
62		(*R*)-*N*-(4-(3-((5-chloro-4-(methylamino)pyrimidin-2-yl)amino)pyrrolidine-1-carbonyl)phenyl)acrylamide
63		(R)-1-(7-(3-((5-chloro-4-methoxypyrimidin-2-yl)amino)pyrrolidine-1-carbonyl)-2H-benzo[b][1,4]oxazin-4(3H)-yl)prop-2-en-1-one
64		(R)-N-(4-(3-((5-chloropyridin-2-yl)amino)pyrrolidine-1-carbonyl)phenyl)acrylamide
65		Synthesis of (R)-1-(6-(3-((5-chloro-4-methoxypyrimidin-2-yl)amino)pyrrolidine-1-carbonyl)-3,4-dihydroquinolin-1(2H)-yl)prop-2-en-1-one
66		(R)-N-(2-chloro-4-(3-((5-chloro-4-methoxypyrimidin-2-yl)amino)pyrrolidine-1-carbonyl)phenyl)acrylamide

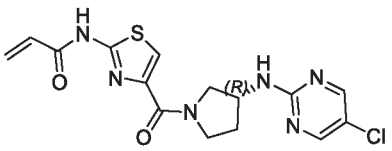
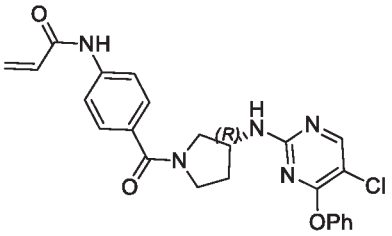
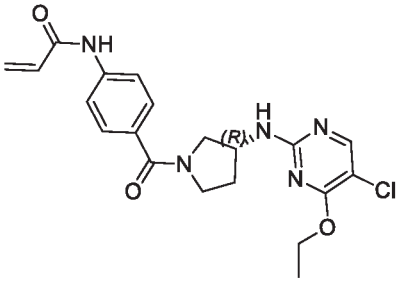
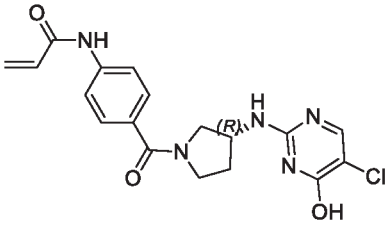
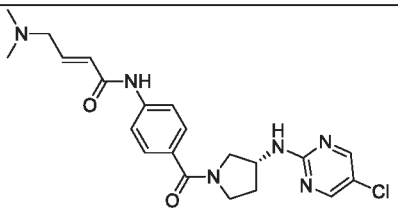
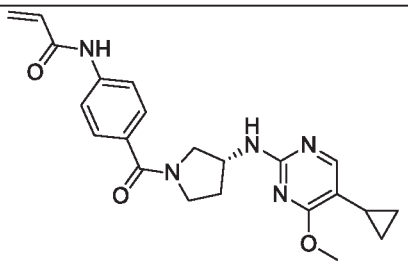
Synthetic Chemistry Example	Compound Structure	Compound Name
67		(R)-N-(4-(3-((5-chloro-4-methoxypyrimidin-2-yl)amino)pyrrolidine-1-carbonyl)thiazol-2-yl)acrylamide
68		(R)-N-(4-(3-((5-chloro-4-methoxypyrimidin-2-yl)amino)pyrrolidine-1-carbonyl)-2-morpholinophenyl)acrylamide
69		(R)-N-(4-(3-((5-chloropyrimidin-2-yl)amino)pyrrolidine-1-carbonyl)-2-(1-methyl-1H-pyrazol-4-yl)phenyl)acrylamide
70		(R)-N-(4-(3-((5-cyanopyrimidin-2-yl)amino)pyrrolidine-1-carbonyl)phenyl)-N-methylacrylamide
71		(R)-N-(4-(3-((4-cyclopropoxy-5-fluoropyrimidin-2-yl)amino)pyrrolidine-1-carbonyl)phenyl)acrylamide
72		(R)-N-(2-chloro-4-(3-((5-chloropyrimidin-2-yl)amino)pyrrolidine-1-carbonyl)phenyl)acrylamide

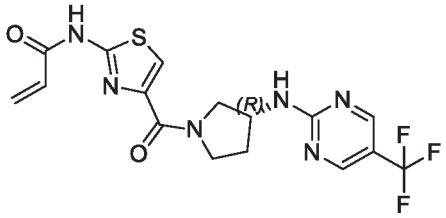
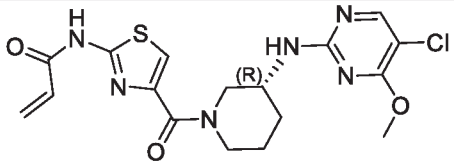
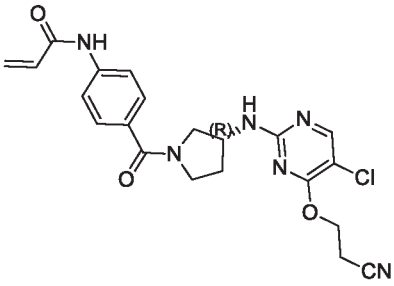
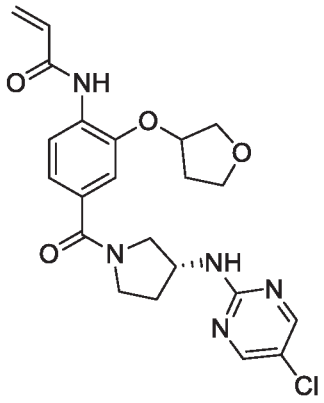
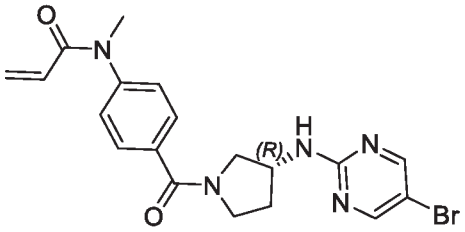
Synthetic Chemistry Example	Compound Structure	Compound Name
73		(R)-N-(5-(3-((5-chloro-4-methoxypyrimidin-2-yl)amino)pyrrolidine-1-carbonyl)thiazol-2-yl)acrylamide
74		(R)-N-(4-(3-((5-chloro-4-methoxypyrimidin-2-yl)amino)pyrrolidine-1-carbonyl)-2-(piperidin-1-yl)phenyl)acrylamide
75		(*R*)-*N*-(4-(3-((5-methylpyridin-2-yl)amino)pyrrolidine-1-carbonyl)phenyl)acrylamide
76		(R)-N-(4-(3-((5-bromopyrimidin-2-yl)amino)pyrrolidine-1-carbonyl)-2-methylphenyl)acrylamide
77		(R)-N-(6-(3-((5-chloro-4-methoxypyrimidin-2-yl)amino)pyrrolidine-1-carbonyl)pyridin-3-yl)-N-methylacrylamide

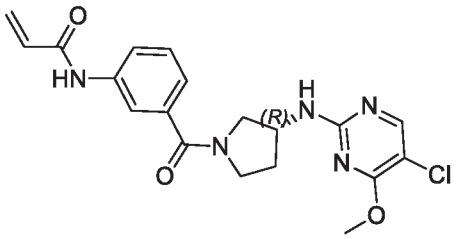
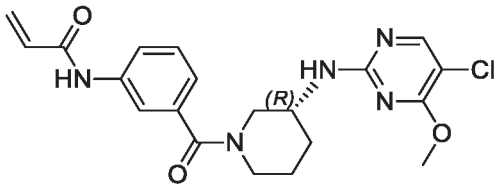
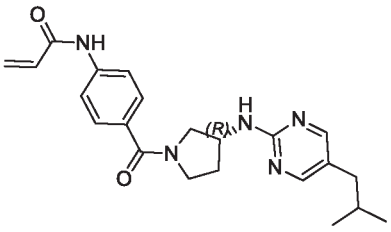
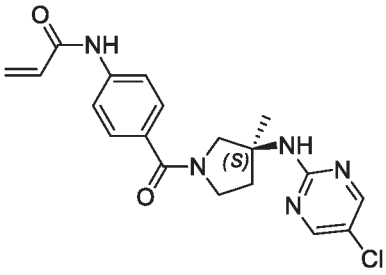
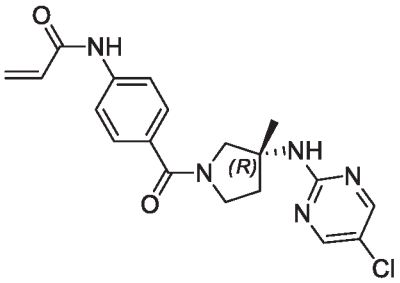
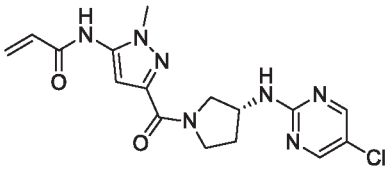
Synthetic Chemistry Example	Compound Structure	Compound Name
78		(R)-N-(4-(3-((5-chloro-4-methoxypyrimidin-2-yl)amino)pyrrolidine-1-carbonyl)-2-(4-methylpiperazin-1-yl)phenyl)acrylamide
79		(*R*)-*N*-(2-methyl-4-(3-((5-(trifluoromethyl)pyrimidin-2-yl)amino)pyrrolidine-1-carbonyl)phenyl)acrylamide
80		(*R*)-*N*-(4-(3-((5-chloro-4-methylpyrimidin-2-yl)amino)pyrrolidine-1-carbonyl)-2-methylphenyl)acrylamide
81		(R)-N-(4-(3-((4-cyclopropoxy-5-methylpyrimidin-2-yl)amino)pyrrolidine-1-carbonyl)phenyl)acrylamide
82		(R)-N-(4-(3-((5-chloro-4-methoxypyrimidin-2-yl)amino)pyrrolidine-1-carbonyl)-2-(1-methyl-1H-pyrazol-4-yl)phenyl)acrylamide

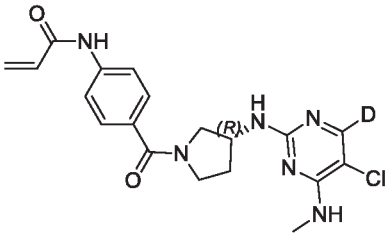
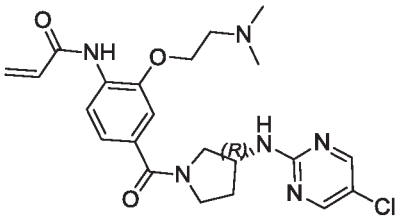
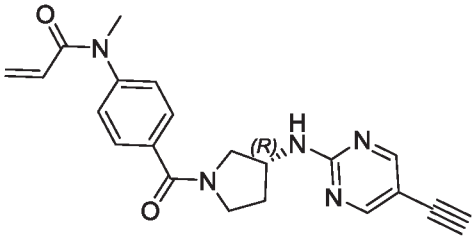
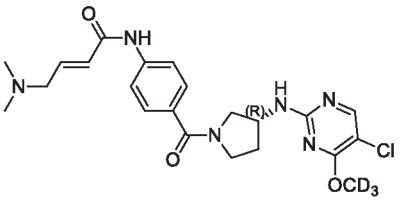
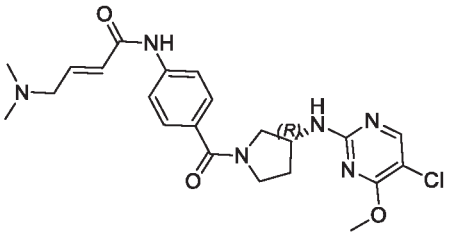
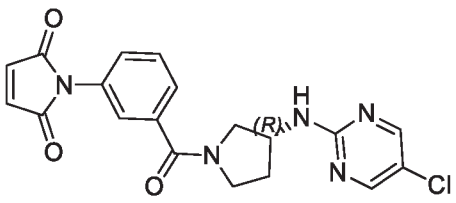
Synthetic Chemistry Example	Compound Structure	Compound Name
83		(*R*)-*N*-(4-(3-((5-chloropyrimidin-2-yl)amino)pyrrolidine-1-carbonyl)phenyl)-2-methylenebutanamide
84		(*R*)-*N*-(4-(3-((5-chloropyrimidin-2-yl)amino)pyrrolidine-1-carbonyl)phenyl)ethenesulfonamide
85		(*R*)-*N*-(4-(3-((5-cyclopropylpyridin-2-yl)amino)pyrrolidine-1-carbonyl)phenyl)acrylamide
86		(*R*)-*N*-(4-(3-((5-chloro-4-(dimethylamino)pyrimidin-2-yl)amino)pyrrolidine-1-carbonyl)phenyl)acrylamide
87		(R)-N-(4-(3-((5-chloropyrimidin-2-yl)amino)pyrrolidine-1-carbonyl)phenyl)acrylamide

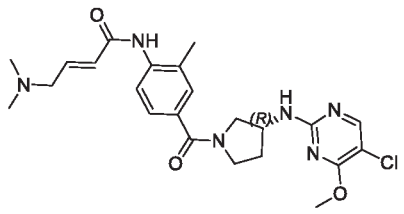
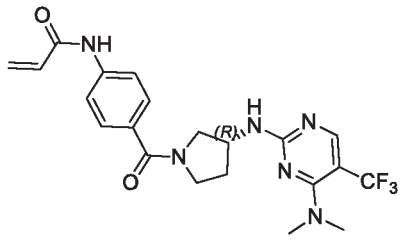
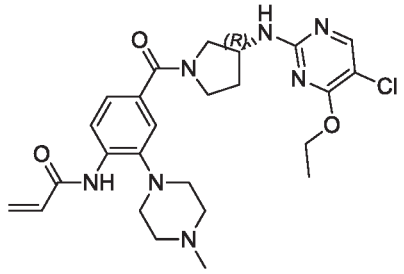
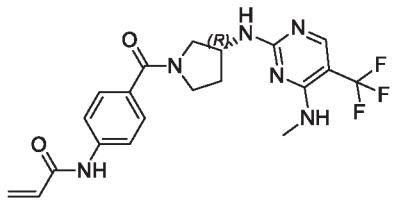
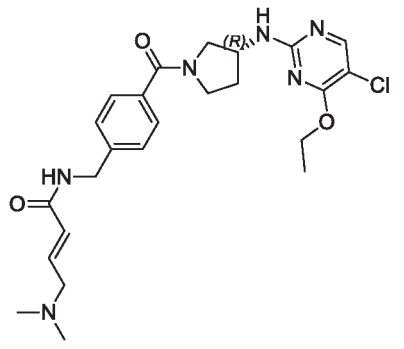
Synthetic Chemistry Example	Compound Structure	Compound Name
88		(R)-N-(4-(3-((5-chloro-4-(2-methoxyethoxy)pyrimidin-2-yl)amino)pyrrolidine-1-carbonyl)phenyl)acrylamide
89		(*R*)-*N*-(4-(3-((4-(azetidin-1-yl)-5-chloropyrimidin-2-yl)amino)pyrrolidine-1-carbonyl)phenyl)acrylamide
90		(R)-N-(4-(3-((4-amino-5-chloropyrimidin-2-yl)amino)pyrrolidine-1-carbonyl)phenyl)acrylamide
91		(R)-N-(4-(3-((4-amino-5-(trifluoromethyl)pyrimidin-2-yl)amino)pyrrolidine-1-carbonyl)phenyl)acrylamide
92		(R)-N-(4-(3-((5-chloro-4-(trifluoromethyl)pyrimidin-2-yl)amino)pyrrolidine-1-carbonyl)phenyl)acrylamide
93		(R)-N-(4-(3-((5-chloro-4-(trideuteromethoxy)pyrimidin-2-yl)amino)pyrrolidine-1-carbonyl)phenyl)acrylamide

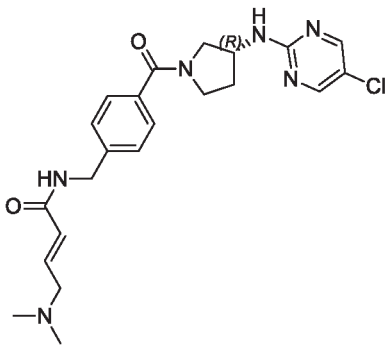
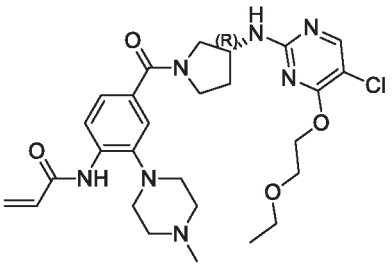
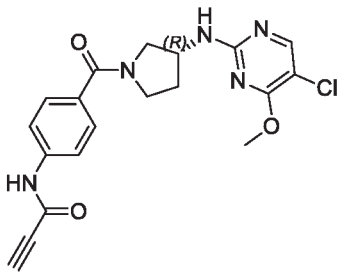
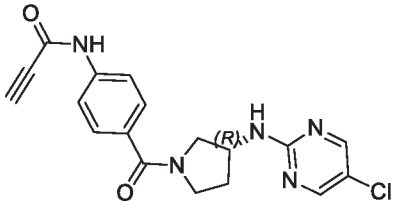
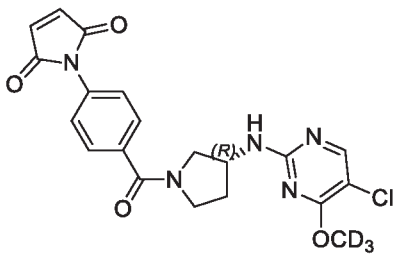
Synthetic Chemistry Example	Compound Structure	Compound Name
94		(R)-N-(4-(3-((5-chloropyrimidin-2-yl)amino)pyrrolidine-1-carbonyl)thiazol-2-yl)acrylamide
95		(*R*)-*N*-(4-(3-((5-chloro-4-phenoxypyrimidin-2-yl)amino)pyrrolidine-1-carbonyl)phenyl)acrylamide
96		(*R*)-*N*-(4-(3-((5-chloro-4-ethoxypyrimidin-2-yl)amino)pyrrolidine-1-carbonyl)phenyl)acrylamide
97		(R)-N-(4-(3-((5-chloro-4-hydroxypyrimidin-2-yl)amino)pyrrolidine-1-carbonyl)phenyl)acrylamide
98		(*R,E*)-*N*-(4-(3-((5-chloropyrimidin-2-yl)amino)pyrrolidine-1-carbonyl)phenyl)-4-(dimethylamino)but-2-enamide
99		(R)-N-(4-(3-((5-cyclopropyl-4-methoxypyrimidin-2-yl)amino)pyrrolidine-1-carbonyl)phenyl)acrylamide

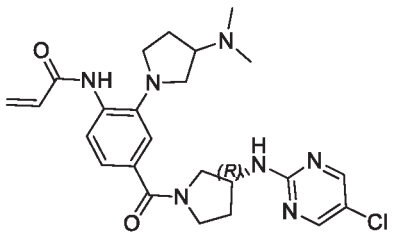
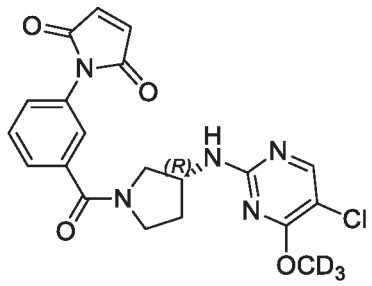
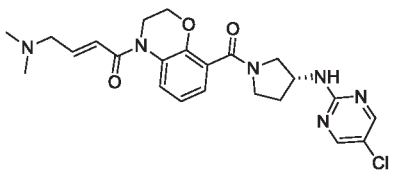
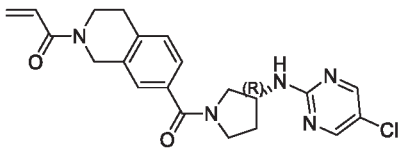
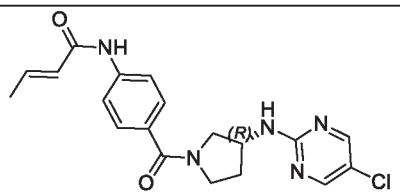
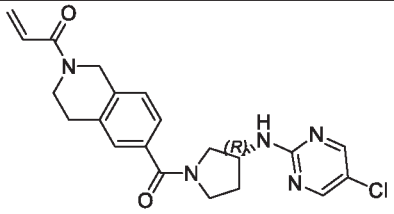
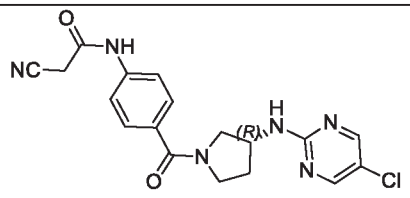
Synthetic Chemistry Example	Compound Structure	Compound Name
100		(*R*)-*N*-(4-(3-((5-(trifluoromethyl)pyrimidin-2-yl)amino)pyrrolidine-1-carbonyl)thiazol-2-yl)acrylamide
101		(*R*)-*N*-(4-(3-((5-chloro-4-methoxypyrimidin-2-yl)amino)piperidine-1-carbonyl)thiazol-2-yl)acrylamide
102		(R)-N-(4-(3-((5-chloro-4-(2-cyanoethoxy)pyrimidin-2-yl)amino)pyrrolidine-1-carbonyl)phenyl)acrylamide
103		*N*-(4-((*R*)-3-((5-chloropyrimidin-2-yl)amino)pyrrolidine-1-carbonyl)-2-((tetrahydrofuran-3-yl)oxy)phenyl)acrylamide
104		(R)-N-(4-(3-((5-bromopyrimidin-2-yl)amino)pyrrolidine-1-carbonyl)phenyl)-N-methylacrylamide

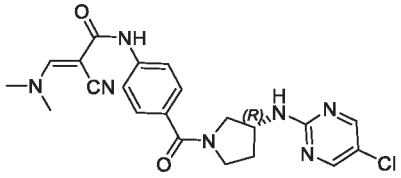
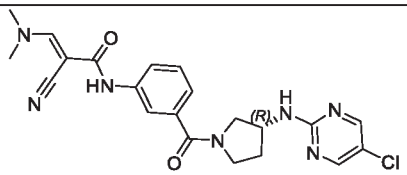
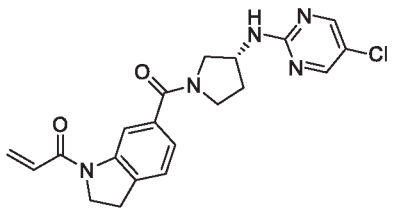
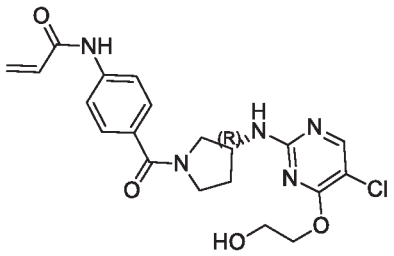
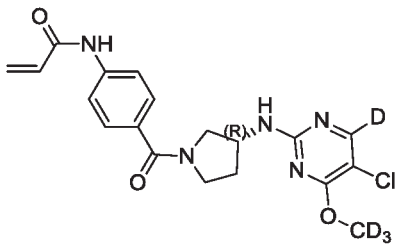
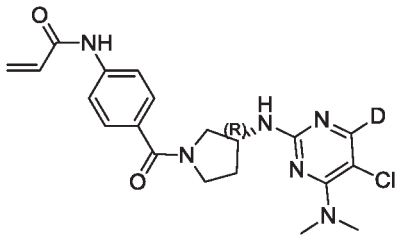
Synthetic Chemistry Example	Compound Structure	Compound Name
105		(*R*)-*N*-(3-(3-((5-chloro-4-methoxypyrimidin-2-yl)amino)pyrrolidine-1-carbonyl)phenyl)acrylamide
106		(*R*)-*N*-(3-(3-((5-chloro-4-methoxypyrimidin-2-yl)amino)piperidine-1-carbonyl)phenyl)acrylamide
107		(*R*)-*N*-(4-(3-((5-isobutylpyrimidin-2-yl)amino)pyrrolidine-1-carbonyl)phenyl)acrylamide
108		(S)-N-(4-(3-((5-chloropyrimidin-2-yl)amino)-3-methylpyrrolidine-1-carbonyl)phenyl)acrylamide
109		(R)-N-(4-(3-((5-cyanopyrimidin-2-yl)amino)pyrrolidine-1-carbonyl)-2-(2-(dimethylamino)ethoxy)phenyl)acrylamide
110		(*R*)-*N*-(3-(3-((5-chloropyrimidin-2-yl)amino)pyrrolidine-1-carbonyl)-1-methyl-1*H*-pyrazol-5-yl)acrylamide

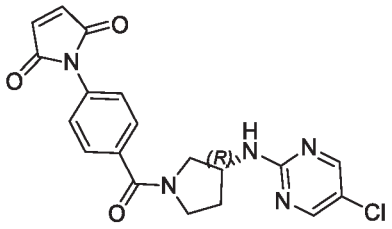
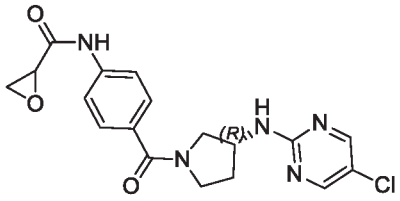
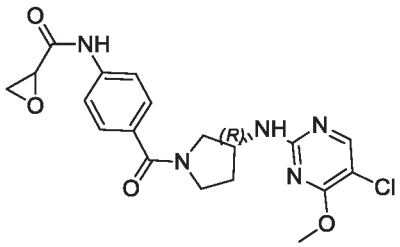
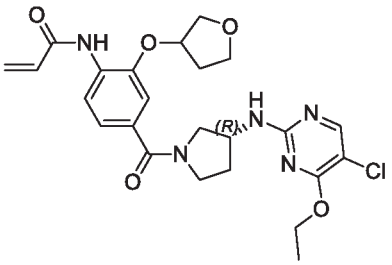
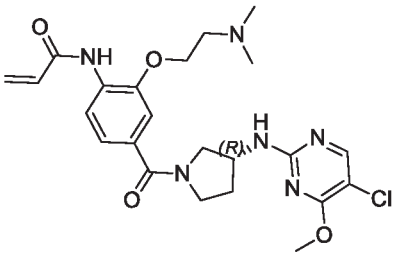
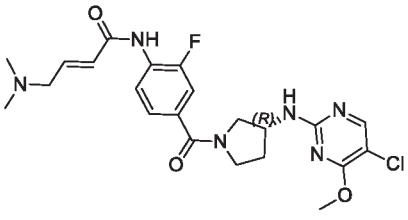
Synthetic Chemistry Example	Compound Structure	Compound Name
111		(R)-N-(4-(3-((4-deutero-5-chloro-6-(methylamino)pyrimidin-2-yl)amino)pyrrolidine-1-carbonyl)phenyl)acrylamide
112		(*R*)-*N*-(4-(3-((5-chloropyrimidin-2-yl)amino)pyrrolidine-1-carbonyl)-2-(2-(dimethylamino)ethoxy)phenyl)acrylamide
113		(R)-N-(4-(3-((5-ethynylpyrimidin-2-yl)amino)pyrrolidine-1-carbonyl)phenyl)-N-methylacrylamide
114		(R,E)-N-(4-(3-((5-chloro-4-(trideuteromethoxy)pyrimidin-2-yl)amino)pyrrolidine-1-carbonyl)phenyl)-4-(dimethylamino)but-2-enamide
115		(*R*,*E*)-*N*-(4-(3-((5-chloro-4-methoxypyrimidin-2-yl)amino)pyrrolidine-1-carbonyl)phenyl)-4-(dimethylamino)but-2-enamide
116		(R)-1-(3-(3-((5-chloropyrimidin-2-yl)amino)pyrrolidine-1-carbonyl)phenyl)-1H-pyrrole-2,5-dione

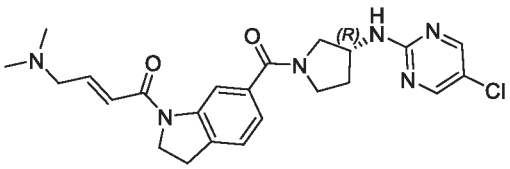
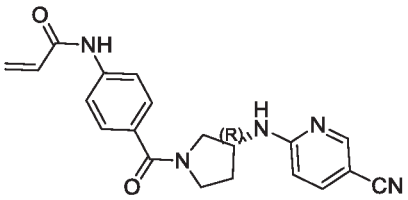
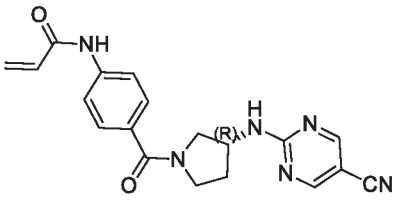
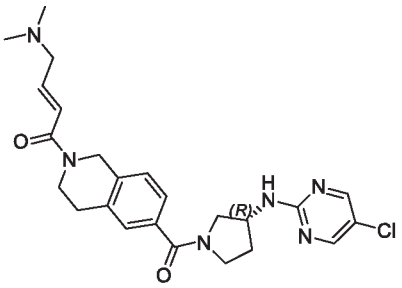
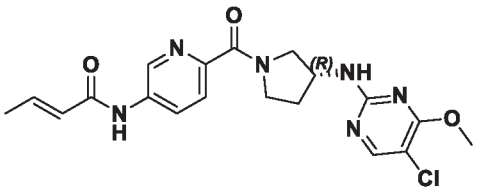
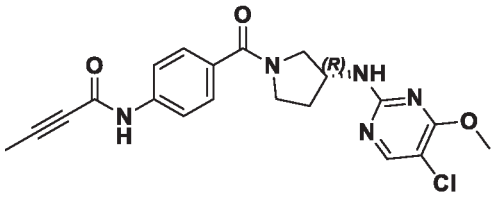
Synthetic Chemistry Example	Compound Structure	Compound Name
117		(*R*,*E*)-*N*-(4-(3-((5-chloro-4-methoxypyrimidin-2-yl)amino)pyrrolidine-1-carbonyl)-2-methylphenyl)-4-(dimethylamino)but-2-enamide
118		(R)-N-(4-(3-((4-(dimethylamino)-5-(trifluoromethyl)pyrimidin-2-yl)amino)pyrrolidine-1-carbonyl)phenyl)acrylamide
119		(R)-N-(4-(3-((5-chloro-4-ethoxypyrimidin-2-yl)amino)pyrrolidine-1-carbonyl)-2-(4-methylpiperazin-1-yl)phenyl)acrylamide
120		(R)-N-(4-(3-((4-(methylamino)-5-(trifluoromethyl)pyrimidin-2-yl)amino)pyrrolidine-1-carbonyl)phenyl)acrylamide
121		(R,E)-N-(4-(3-((5-chloro-4-ethoxypyrimidin-2-yl)amino)pyrrolidine-1-carbonyl)benzyl)-4-(dimethylamino)but-2-enamide

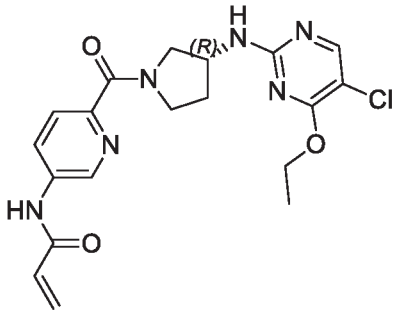
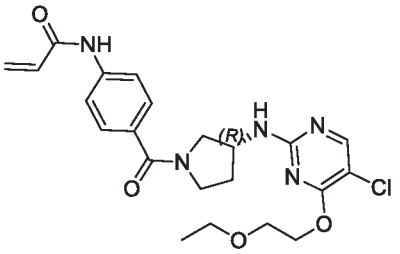
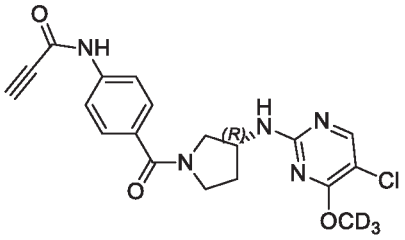
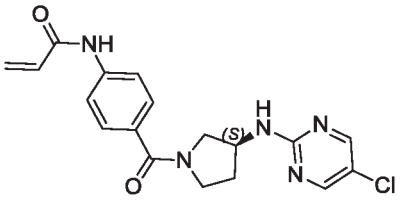
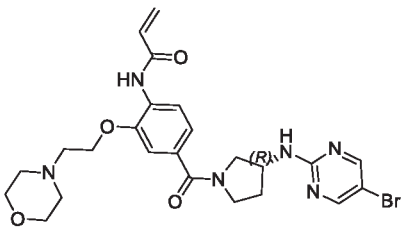
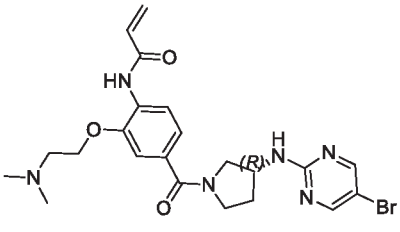
Synthetic Chemistry Example	Compound Structure	Compound Name
122		(R,E)-N-(4-(3-((5-chloropyrimidin-2-yl)amino)pyrrolidine-1-carbonyl)benzyl)-4-(dimethylamino)but-2-enamide
123		(R)-N-(4-(3-((5-chloro-4-(2-ethoxyethoxy)pyrimidin-2-yl)amino)pyrrolidine-1-carbonyl)-2-(4-methylpiperazin-1-yl)phenyl)acrylamide
124		(R)-N-(4-(3-((5-chloro-4-methoxypyrimidin-2-yl)amino)pyrrolidine-1-carbonyl)phenyl)propiolamide
125		(*R*)-*N*-(4-(3-((5-chloropyrimidin-2-yl)amino)pyrrolidine-1-carbonyl)phenyl)propiolamide
126		(R)-1-(4-(3-((5-chloro-4-(trideuteromethoxy)pyrimidin-2-yl)amino)pyrrolidine-1-carbonyl)phenyl)-1H-pyrrole-2,5-dione

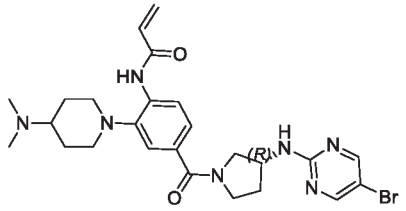
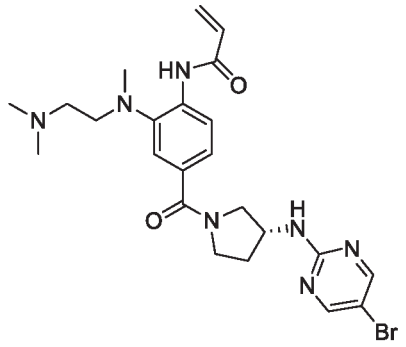
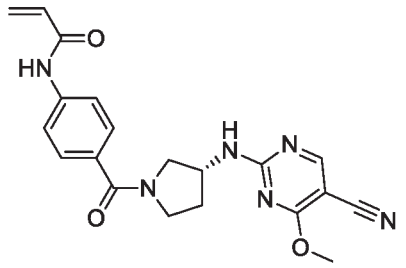
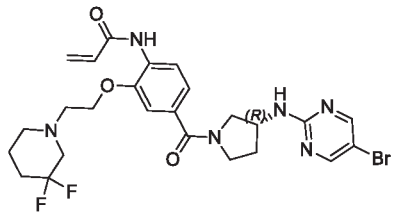
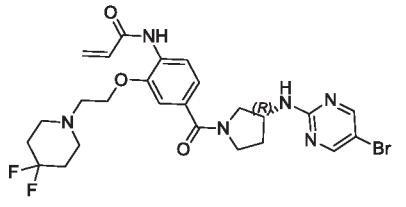
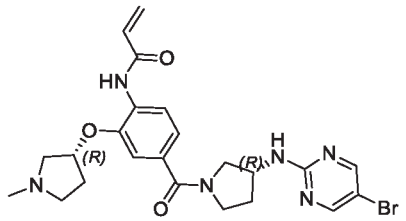
Synthetic Chemistry Example	Compound Structure	Compound Name
127		*N*-(4-((*R*)-3-((5-chloropyrimidin-2-yl)amino)pyrrolidine-1-carbonyl)-2-(3-(dimethylamino)pyrrolidin-1-yl)phenyl)acrylamide
128		(R)-1-(3-(3-((5-chloro-4-(trideuteriomethoxy)pyrimidin-2-yl)amino)pyrrolidine-1-carbonyl)phenyl)-1H-pyrrole-2,5-dione
129		(*R*,*E*)-1-(8-(3-((5-chloropyrimidin-2-yl)amino)pyrrolidine-1-carbonyl)-2H-benzo[b][1,4]oxazin-4(3H)-yl)-4-(dimethylamino)but-2-en-1-one
130		(*R*)-1-(7-(3-((5-chloropyrimidin-2-yl)amino)pyrrolidine-1-carbonyl)-3,4-dihydroisoquinolin-2(1*H*)-yl)prop-2-en-1-one
131		(*R*,*E*)-*N*-(4-(3-((5-chloropyrimidin-2-yl)amino)pyrrolidine-1-carbonyl)phenyl)but-2-enamide
132		(*R*)-1-(6-(3-((5-chloropyrimidin-2-yl)amino)pyrrolidine-1-carbonyl)-3,4-dihydroisoquinolin-2(1*H*)-yl)prop-2-en-1-one
133		(*R*)-*N*-(4-(3-((5-chloropyrimidin-2-yl)amino)pyrrolidine-1-carbonyl)phenyl)-2-cyanoacetamide

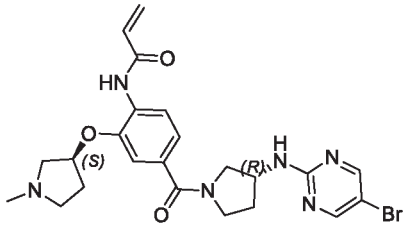
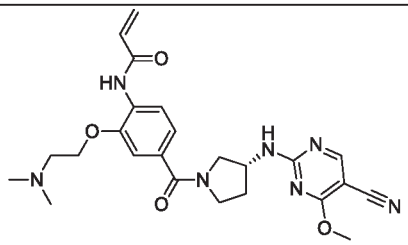
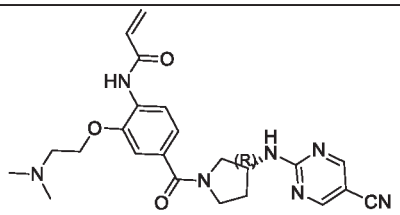
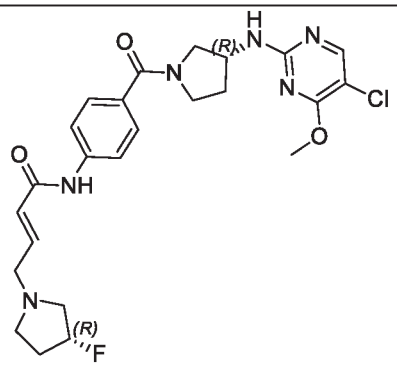
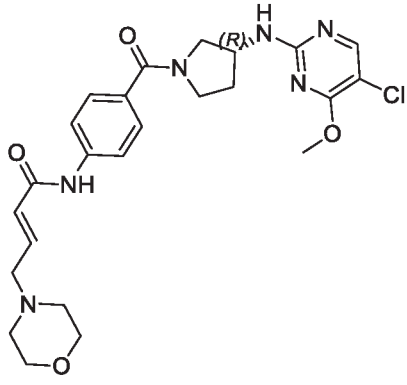
Synthetic Chemistry Example	Compound Structure	Compound Name
134		(*R*)-*N*-(4-(3-((5-chloropyrimidin-2-yl)amino)pyrrolidine-1-carbonyl)phenyl)-2-cyano-3-(dimethylamino)acrylamide
135		(R)-N-(3-(3-((5-chloropyrimidin-2-yl)amino)pyrrolidine-1-carbonyl)phenyl)-2-cyano-3-(dimethylamino)acrylamide
136		(*R*)-1-(6-(3-((5-chloropyrimidin-2-yl)amino)pyrrolidine-1-carbonyl)indolin-1-yl)prop-2-en-1-one
137		(*R*)-*N*-(4-(3-((5-chloro-4-(2-hydroxyethoxy)pyrimidin-2-yl)amino)pyrrolidine-1-carbonyl)phenyl)acrylamide
138		(R)-N-(4-(3-((4-deutero-5-chloro-6-(trideuteromethoxy)pyrimidin-2-yl)amino)pyrrolidine-1-carbonyl)phenyl)acrylamide
139		(R)-N-(4-(3-((4-deutero-5-chloro-6-(dimethylamino)pyrimidin-2-yl)amino)pyrrolidine-1-carbonyl)phenyl)acrylamide

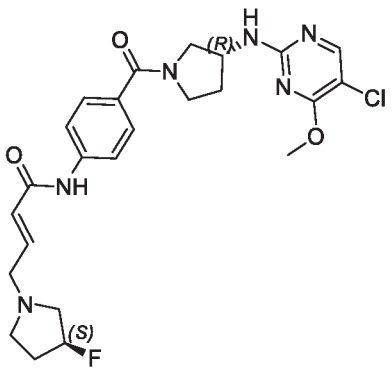
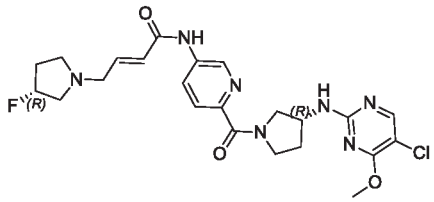
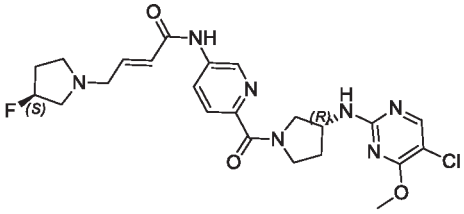
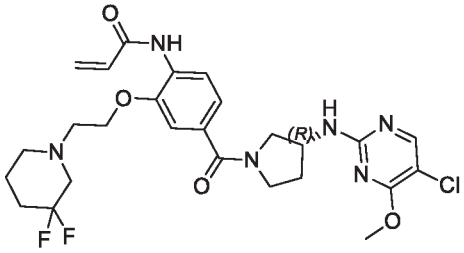
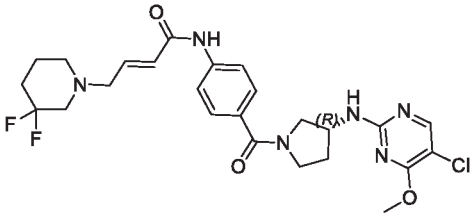
Synthetic Chemistry Example	Compound Structure	Compound Name
140		(R)-1-(4-(3-((5-chloropyrimidin-2-yl)amino)pyrrolidine-1-carbonyl)phenyl)-1H-pyrrole-2,5-dione
141		*N*-(4-((*R*)-3-((5-chloropyrimidin-2-yl)amino)pyrrolidine-1-carbonyl)phenyl)oxirane-2-carboxamide
142		*N*-(4-((*R*)-3-((5-chloro-4-methoxypyrimidin-2-yl)amino)pyrrolidine-1-carbonyl)phenyl)oxirane-2-carboxamide
143		N-(4-((R)-3-((5-chloro-4-ethoxypyrimidin-2-yl)amino)pyrrolidine-1-carbonyl)-2-((tetrahydrofuran-3-yl)oxy)phenyl)acrylamide
144		(R)-N-(4-(3-((5-chloro-4-ethoxypyrimidin-2-yl)amino)pyrrolidine-1-carbonyl)-2-(2-(dimethylamino)ethoxy)phenyl)acrylamide
145		(*R*,*E*)-*N*-(4-(3-((5-chloro-4-methoxypyrimidin-2-yl)amino)pyrrolidine-1-carbonyl)-2-fluorophenyl)-4-(dimethylamino)but-2-enamide

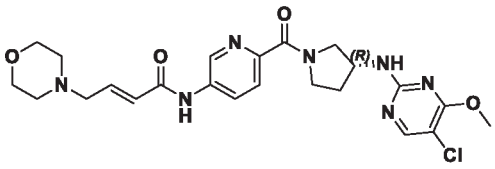
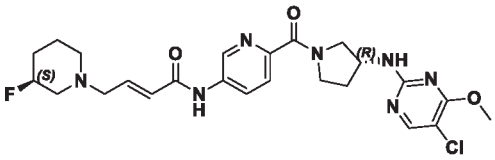
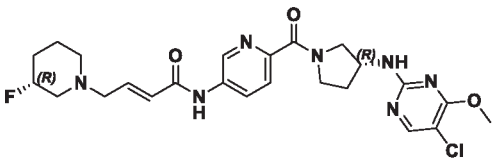
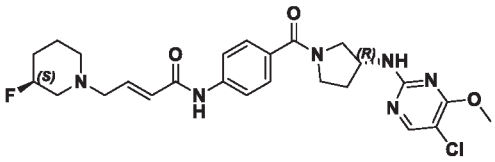
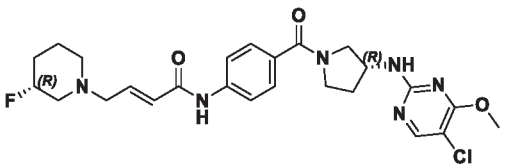
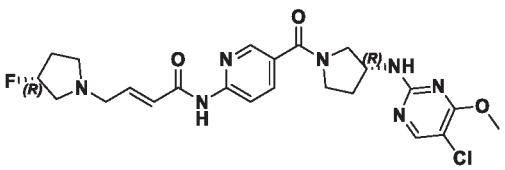
Synthetic Chemistry Example	Compound Structure	Compound Name
146		(*R*,*E*)-1-(6-(3-((5-chloropyrimidin-2-yl)amino)pyrrolidine-1-carbonyl)indolin-1-yl)-4-(dimethylamino)but-2-en-1-one
147		(R)-N-(4-(3-((5-cyanopyridin-2-yl)amino)pyrrolidine-1-carbonyl)phenyl)acrylamide
148		(R)-N-(4-(3-((5-cyanopyrimidin-2-yl)amino)pyrrolidine-1-carbonyl)phenyl)acrylamide
149		(*R*,*E*)-1-(6-(3-((5-chloropyrimidin-2-yl)amino)pyrrolidine-1-carbonyl)-3,4-dihydroisoquinolin-2(1*H*)-yl)-4-(dimethylamino)but-2-en-1-one
150		(R,E)-N-(6-(3-((5-chloro-4-methoxypyrimidin-2-yl)amino)pyrrolidine-1-carbonyl)pyridin-3-yl)but-2-enamide
151		(R)-N-(4-(3-((5-chloro-4-methoxypyrimidin-2-yl)amino)pyrrolidine-1-carbonyl)phenyl)but-2-ynamide

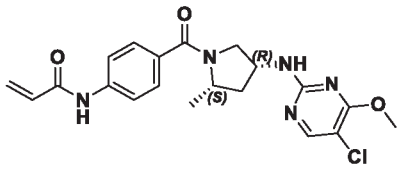
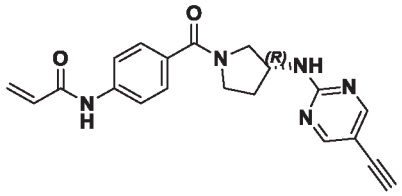
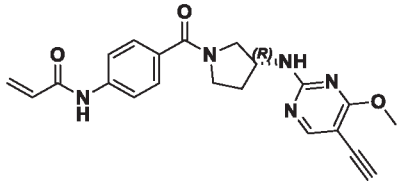
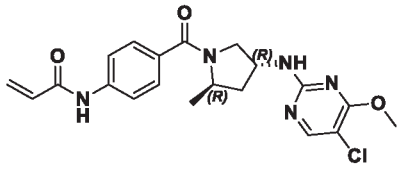
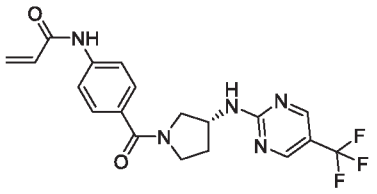
Synthetic Chemistry Example	Compound Structure	Compound Name
152		(R)-N-(6-(3-((5-chloro-4-ethoxypyrimidin-2-yl)amino)pyrrolidine-1-carbonyl)pyridin-3-yl)acrylamide
153		(R)-N-(4-(3-((5-chloro-4-(2-ethoxyethoxy)pyrimidin-2-yl)amino)pyrrolidine-1-carbonyl)phenyl)acrylamide
154		(R)-N-(4-(3-((5-chloro-4-(trideuteromethoxy)pyrimidin-2-yl)amino)pyrrolidine-1-carbonyl)phenyl)propiolamide
155		(S)-N-(4-(3-((5-chloropyrimidin-2-yl)amino)pyrrolidine-1-carbonyl)phenyl)acrylamide
156		(R)-N-(4-(3-((5-bromopyrimidin-2-yl)amino)pyrrolidine-1-carbonyl)-2-(2-morpholinoethoxy)phenyl)acrylamide
157		(R)-N-(4-(3-((5-bromopyrimidin-2-yl)amino)pyrrolidine-1-carbonyl)-2-(2-(dimethylamino)ethoxy)phenyl)acrylamide

Synthetic Chemistry Example	Compound Structure	Compound Name
158		(R)-N-(4-(3-((5-bromopyrimidin-2-yl)amino)pyrrolidine-1-carbonyl)-2-(4-(dimethylamino)piperidin-1-yl)phenyl)acrylamide
159		(R)-N-(4-(3-((5-bromopyrimidin-2-yl)amino)pyrrolidine-1-carbonyl)-2-((2-(dimethylamino)ethyl)(methyl)amino)phenyl)acrylamide
160		(R)-N-(4-(3-((5-cyano-4-methoxypyrimidin-2-yl)amino)pyrrolidine-1-carbonyl)phenyl)acrylamide
161		(R)-N-(4-(3-((5-bromopyrimidin-2-yl)amino)pyrrolidine-1-carbonyl)-2-(2-(3,3-difluoropiperidin-1-yl)ethoxy)phenyl)acrylamide
162		(R)-N-(4-(3-((5-bromopyrimidin-2-yl)amino)pyrrolidine-1-carbonyl)-2-(2-(4,4-difluoropiperidin-1-yl)ethoxy)phenyl)acrylamide
163		N-(4-((R)-3-((5-bromopyrimidin-2-yl)amino)pyrrolidine-1-carbonyl)-2-(((R)-1-methylpyrrolidin-3-yl)oxy)phenyl)acrylamide

Synthetic Chemistry Example	Compound Structure	Compound Name
164		N-(4-((R)-3-((5-bromopyrimidin-2-yl)amino)pyrrolidine-1-carbonyl)-2-(((S)-1-methylpyrrolidin-3-yl)oxy)phenyl)acrylamide
165		(R)-N-(4-(3-((5-cyano-4-methoxypyrimidin-2-yl)amino)pyrrolidine-1-carbonyl)-2-(2-(dimethylamino)ethoxy)phenyl)acrylamide
166		(R)-N-(4-(3-((5-cyanopyrimidin-2-yl)amino)pyrrolidine-1-carbonyl)-2-(2-(dimethylamino)ethoxy)phenyl)acrylamide
167		(E)-N-(4-((R)-3-((5-chloro-4-methoxypyrimidin-2-yl)amino)pyrrolidine-1-carbonyl)phenyl)-4-((R)-3-fluoropyrrolidin-1-yl)but-2-enamide
168		(R,E)-N-(4-(3-((5-chloro-4-methoxypyrimidin-2-yl)amino)pyrrolidine-1-carbonyl)phenyl)-4-morpholinobut-2-enamide

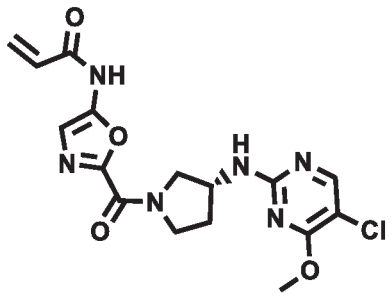
Synthetic Chemistry Example	Compound Structure	Compound Name
169		(E)-N-(4-((R)-3-((5-chloro-4-methoxypyrimidin-2-yl)amino)pyrrolidine-1-carbonyl)phenyl)-4-((S)-3-fluoropyrrolidin-1-yl)but-2-enamide
170		(E)-N-(6-((R)-3-((5-chloro-4-methoxypyrimidin-2-yl)amino)pyrrolidine-1-carbonyl)pyridin-3-yl)-4-((R)-3-fluoropyrrolidin-1-yl)but-2-enamide
171		(E)-N-(6-((R)-3-((5-chloro-4-methoxypyrimidin-2-yl)amino)pyrrolidine-1-carbonyl)pyridin-3-yl)-4-((S)-3-fluoropyrrolidin-1-yl)but-2-enamide
172		(R,E)-N-(6-(3-((5-chloro-4-methoxypyrimidin-2-yl)amino)pyrrolidine-1-carbonyl)pyridin-3-yl)-4-(3,3-difluoropiperidin-1-yl)but-2-enamide
173		(R,E)-N-(4-(3-((5-chloro-4-methoxypyrimidin-2-yl)amino)pyrrolidine-1-carbonyl)phenyl)-4-(3,3-difluoropiperidin-1-yl)but-2-enamide

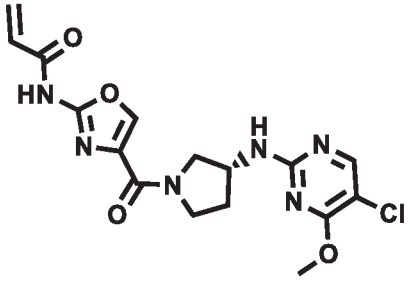
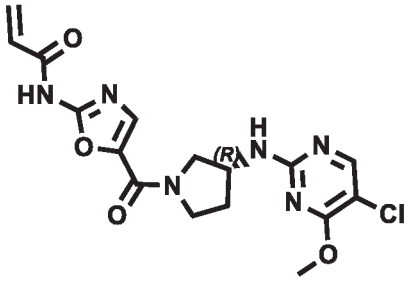
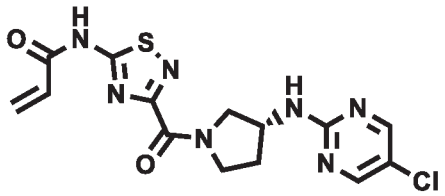
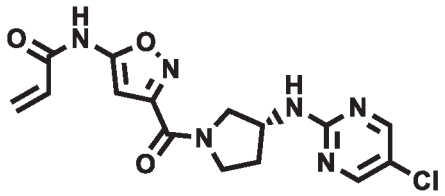
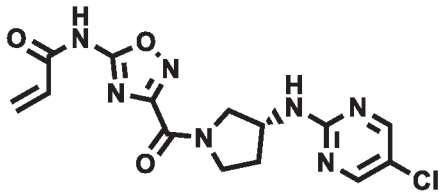
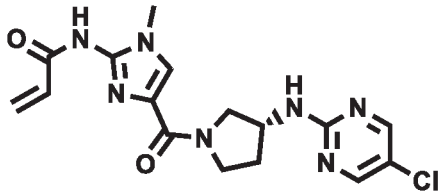
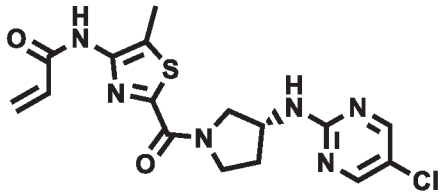
Synthetic Chemistry Example	Compound Structure	Compound Name
174		(R,E)-N-(6-(3-((5-chloro-4-methoxypyrimidin-2-yl)amino)pyrrolidine-1-carbonyl)pyridin-3-yl)-4-morpholinobut-2-enamide
175		(E)-N-(6-((R)-3-((5-chloro-4-methoxypyrimidin-2-yl)amino)pyrrolidine-1-carbonyl)pyridin-3-yl)-4-((S)-3-fluoropiperidin-1-yl)but-2-enamide
176		(E)-N-(6-((R)-3-((5-chloro-4-methoxypyrimidin-2-yl)amino)pyrrolidine-1-carbonyl)pyridin-3-yl)-4-((R)-3-fluoropiperidin-1-yl)but-2-enamide
177		(E)-N-(4-((R)-3-((5-chloro-4-methoxypyrimidin-2-yl)amino)pyrrolidine-1-carbonyl)phenyl)-4-((S)-3-fluoropiperidin-1-yl)but-2-enamide
178		(E)-N-(4-((R)-3-((5-chloro-4-methoxypyrimidin-2-yl)amino)pyrrolidine-1-carbonyl)phenyl)-4-((R)-3-fluoropiperidin-1-yl)but-2-enamide
179		(E)-N-(5-((R)-3-((5-chloro-4-methoxypyrimidin-2-yl)amino)pyrrolidine-1-carbonyl)pyridin-2-yl)-4-((R)-3-fluoropyrrolidin-1-yl)but-2-enamide

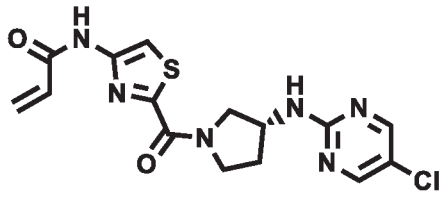
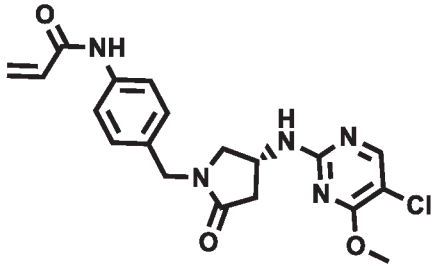
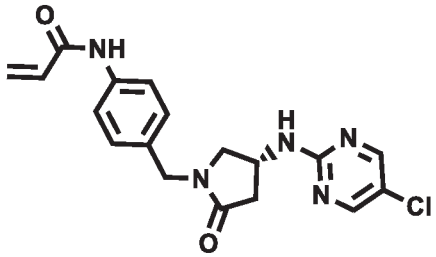
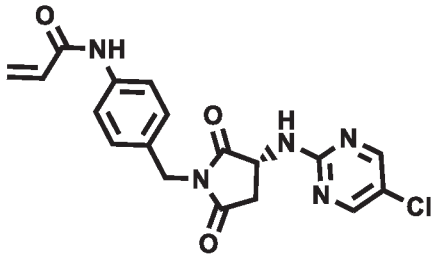
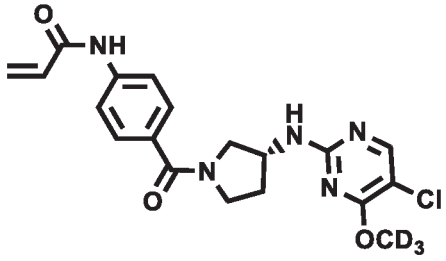
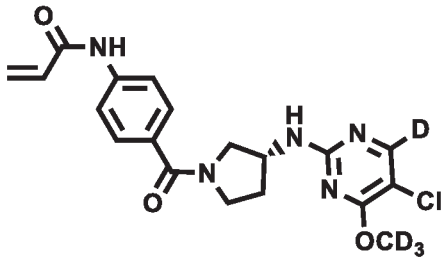
Synthetic Chemistry Example	Compound Structure	Compound Name
180		N-(4-((2S,4R)-4-((5-chloro-4-methoxypyrimidin-2-yl)amino)-2-methylpyrrolidine-1-carbonyl)phenyl)acrylamide
181		(R)-N-(4-(3-((5-ethynylpyrimidin-2-yl)amino)pyrrolidine-1-carbonyl)phenyl)acrylamide
182		(R)-N-(4-(3-((5-ethynyl-4-methoxypyrimidin-2-yl)amino)pyrrolidine-1-carbonyl)phenyl)acrylamide
183		N-(4-((2R,4R)-4-((5-chloro-4-methoxypyrimidin-2-yl)amino)-2-methylpyrrolidine-1-carbonyl)phenyl)acrylamide
184		(R)-N-(4-(3-((5-(trifluoromethyl)pyrimidin-2-yl)amino)pyrrolidine-1-carbonyl)phenyl)acrylamide

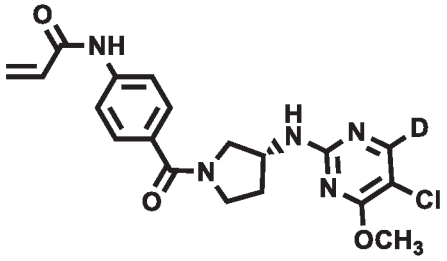
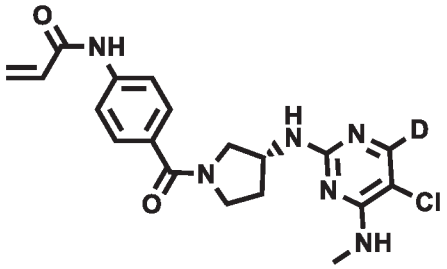
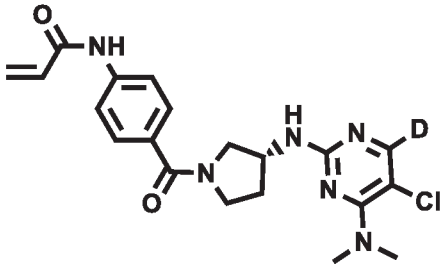
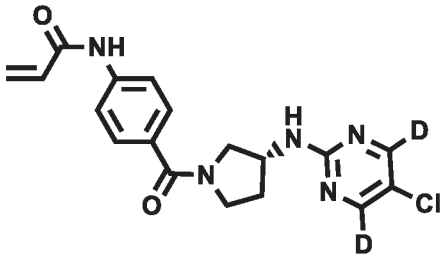
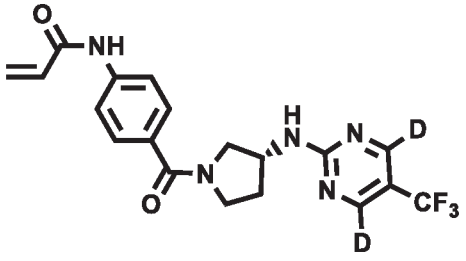
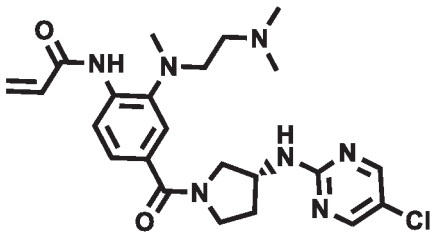
[00188] In some embodiments, the heteroaromatic CDK inhibitory compound of Formula (I) or Formula (II) described herein has a structure provided in Table 2.

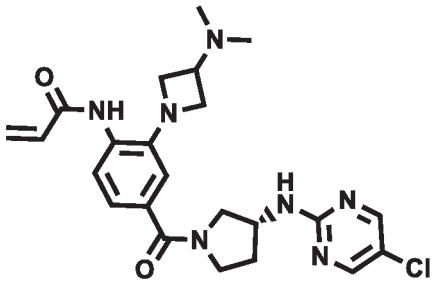
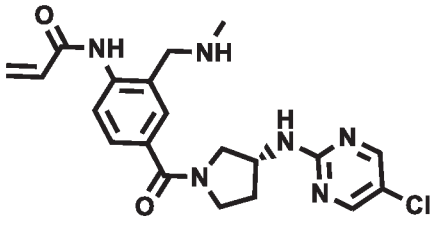
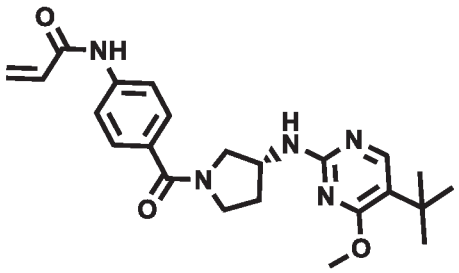
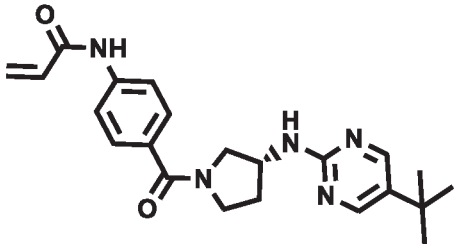
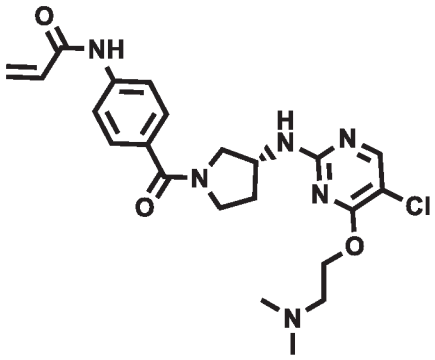
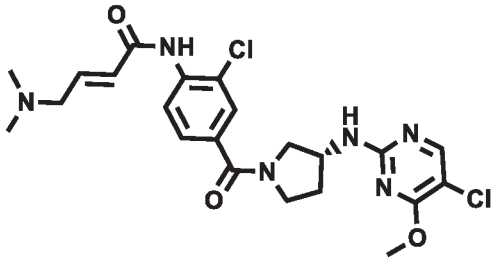
Table 2

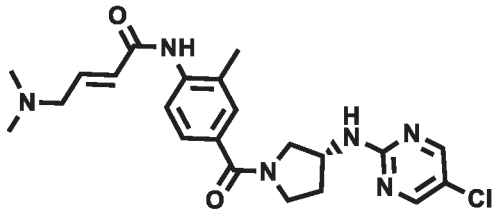
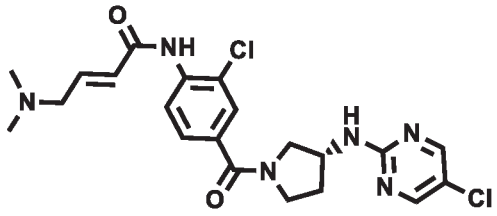
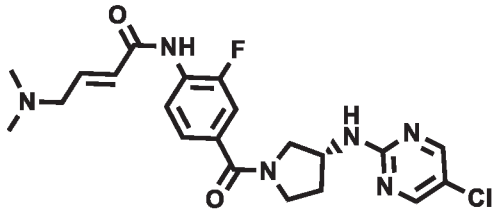
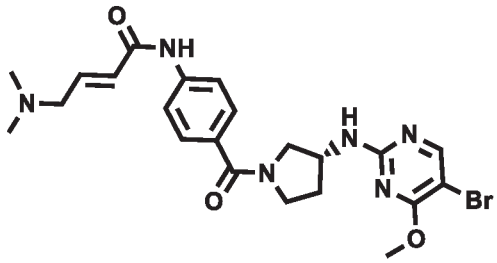
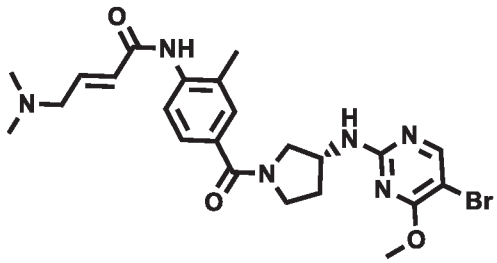
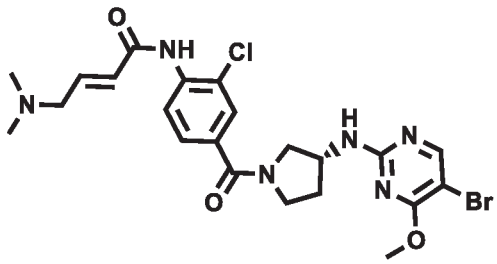
Compound Structure	Compound Name
	(R)-N-(2-(3-((5-chloro-4-methoxypyrimidin-2-yl)amino)pyrrolidine-1-carbonyl)oxazol-5-yl)acrylamide

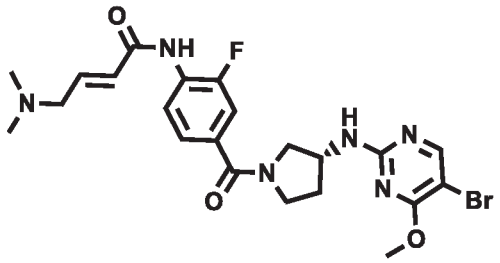
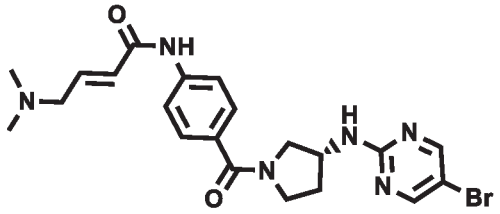
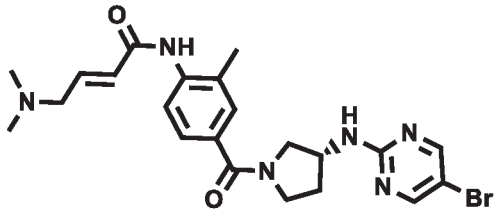
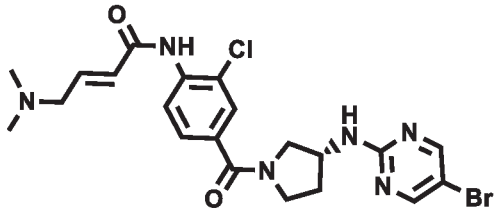
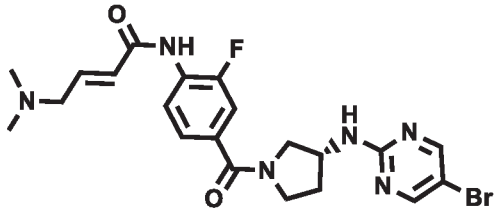
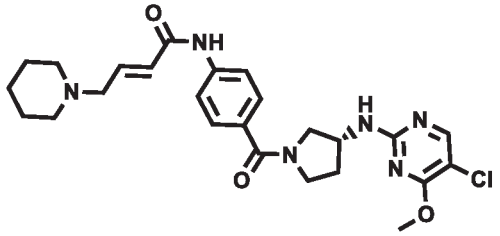
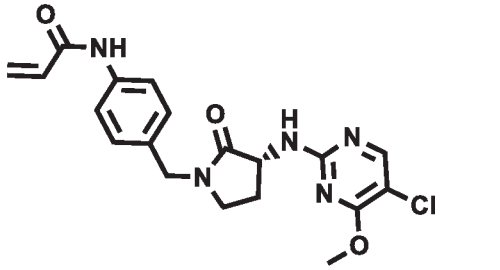
Compound Structure	Compound Name
	(R)-N-(4-(3-((5-chloro-4-methoxypyrimidin-2-yl)amino)pyrrolidine-1-carbonyl)oxazol-2-yl)acrylamide
	(R)-N-(5-(3-((5-chloro-4-methoxypyrimidin-2-yl)amino)pyrrolidine-1-carbonyl)oxazol-2-yl)acrylamide
	(R)-N-(3-(3-((5-chloropyrimidin-2-yl)amino)pyrrolidine-1-carbonyl)-1,2,4-thiadiazol-5-yl)acrylamide
	(R)-N-(3-(3-((5-chloropyrimidin-2-yl)amino)pyrrolidine-1-carbonyl)isoxazol-5-yl)acrylamide
	(R)-N-(3-(3-((5-chloropyrimidin-2-yl)amino)pyrrolidine-1-carbonyl)-1,2,4-oxadiazol-5-yl)acrylamide
	(R)-N-(4-(3-((5-chloropyrimidin-2-yl)amino)pyrrolidine-1-carbonyl)-1-methyl-1H-imidazol-2-yl)acrylamide
	(R)-N-(2-(3-((5-chloropyrimidin-2-yl)amino)pyrrolidine-1-carbonyl)-5-methylthiazol-4-yl)acrylamide

Compound Structure	Compound Name
	(R)-N-(2-(3-((5-chloropyrimidin-2-yl)amino)pyrrolidine-1-carbonyl)thiazol-4-yl)acrylamide
	(R)-N-(4-((4-((5-chloro-4-methoxypyrimidin-2-yl)amino)-2-oxopyrrolidin-1-yl)methyl)phenyl)acrylamide
	(R)-N-(4-((4-((5-chloropyrimidin-2-yl)amino)-2-oxopyrrolidin-1-yl)methyl)phenyl)acrylamide
	(R)-N-(4-((3-((5-chloropyrimidin-2-yl)amino)-2,5-dioxopyrrolidin-1-yl)methyl)phenyl)acrylamide
	(R)-N-(4-(3-((5-chloro-4-(methoxy-d3)pyrimidin-2-yl)amino)pyrrolidine-1-carbonyl)phenyl)acrylamide
	(R)-N-(4-(3-((5-chloro-4-(methoxy-d3)pyrimidin-2-yl-6-d)amino)pyrrolidine-1-carbonyl)phenyl)acrylamide

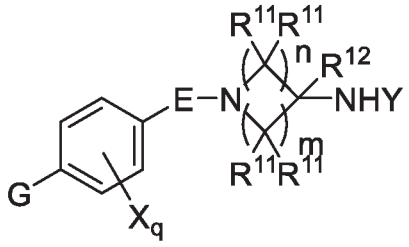
Compound Structure	Compound Name
	(R)-N-(4-(3-((5-chloro-4-methoxypyrimidin-2-yl-6-d)amino)pyrrolidine-1-carbonyl)phenyl)acrylamide
	(R)-N-(4-(3-((5-chloro-4-(methylamino)pyrimidin-2-yl-6-d)amino)pyrrolidine-1-carbonyl)phenyl)acrylamide
	(R)-N-(4-(3-((5-chloro-4-(dimethylamino)pyrimidin-2-yl-6-d)amino)pyrrolidine-1-carbonyl)phenyl)acrylamide
	(R)-N-(4-(3-((5-chloropyrimidin-2-yl-4,6-d2)amino)pyrrolidine-1-carbonyl)phenyl)acrylamide
	(R)-N-(4-(3-((5-(trifluoromethyl)pyrimidin-2-yl-4,6-d2)amino)pyrrolidine-1-carbonyl)phenyl)acrylamide
	(R)-N-(4-(3-((5-chloropyrimidin-2-yl)amino)pyrrolidine-1-carbonyl)-2-((2-(dimethylamino)ethyl)(methyl)amino)phenyl)acrylamide

Compound Structure	Compound Name
	(R)-N-(4-(3-((5-chloropyrimidin-2-yl)amino)pyrrolidine-1-carbonyl)-2-(3-(dimethylamino)azetidin-1-yl)phenyl)acrylamide
	(R)-N-(4-(3-((5-chloropyrimidin-2-yl)amino)pyrrolidine-1-carbonyl)-2-((methylamino)methyl)phenyl)acrylamide
	(R)-N-(4-(3-((5-(tert-butyl)-4-methoxypyrimidin-2-yl)amino)pyrrolidine-1-carbonyl)phenyl)acrylamide
	(R)-N-(4-(3-((5-(tert-butyl)pyrimidin-2-yl)amino)pyrrolidine-1-carbonyl)phenyl)acrylamide
	(R)-N-(4-(3-((5-chloro-4-(2-(dimethylamino)ethoxy)pyrimidin-2-yl)amino)pyrrolidine-1-carbonyl)phenyl)acrylamide
	(R,E)-N-(2-chloro-4-(3-((5-chloro-4-methoxypyrimidin-2-yl)amino)pyrrolidine-1-carbonyl)phenyl)-4-(dimethylamino)but-2-enamide

Compound Structure	Compound Name
	(R,E)-N-(4-(3-((5-chloropyrimidin-2-yl)amino)pyrrolidine-1-carbonyl)-2-methylphenyl)-4-(dimethylamino)but-2-enamide
	(R,E)-N-(2-chloro-4-(3-((5-chloropyrimidin-2-yl)amino)pyrrolidine-1-carbonyl)phenyl)-4-(dimethylamino)but-2-enamide
	(R,E)-N-(4-(3-((5-chloropyrimidin-2-yl)amino)pyrrolidine-1-carbonyl)-2-fluorophenyl)-4-(dimethylamino)but-2-enamide
	(R,E)-N-(4-(3-((5-bromo-4-methoxypyrimidin-2-yl)amino)pyrrolidine-1-carbonyl)phenyl)-4-(dimethylamino)but-2-enamide
	(R,E)-N-(4-(3-((5-bromo-4-methoxypyrimidin-2-yl)amino)pyrrolidine-1-carbonyl)-2-methylphenyl)-4-(dimethylamino)but-2-enamide
	(R,E)-N-(4-(3-((5-bromo-4-methoxypyrimidin-2-yl)amino)pyrrolidine-1-carbonyl)-2-chlorophenyl)-4-(dimethylamino)but-2-enamide

Compound Structure	Compound Name
	(R,E)-N-(4-(3-((5-bromo-4-methoxypyrimidin-2-yl)amino)pyrrolidine-1-carbonyl)-2-fluorophenyl)-4-(dimethylamino)but-2-enamide
	(R,E)-N-(4-(3-((5-bromopyrimidin-2-yl)amino)pyrrolidine-1-carbonyl)phenyl)-4-(dimethylamino)but-2-enamide
	(R,E)-N-(4-(3-((5-bromopyrimidin-2-yl)amino)pyrrolidine-1-carbonyl)-2-methylphenyl)-4-(dimethylamino)but-2-enamide
	(R,E)-N-(4-(3-((5-bromopyrimidin-2-yl)amino)pyrrolidine-1-carbonyl)-2-chlorophenyl)-4-(dimethylamino)but-2-enamide
	(R,E)-N-(4-(3-((5-bromopyrimidin-2-yl)amino)pyrrolidine-1-carbonyl)-2-fluorophenyl)-4-(dimethylamino)but-2-enamide
	(R,E)-N-(4-(3-((5-chloro-4-methoxypyrimidin-2-yl)amino)pyrrolidine-1-carbonyl)phenyl)-4-(piperidin-1-yl)but-2-enamide
	(R)-N-(4-((3-((5-chloro-4-methoxypyrimidin-2-yl)amino)-2-oxopyrrolidin-1-yl)methyl)phenyl)acrylamide

[00189] One embodiment provides a compound, or pharmaceutically acceptable salt or solvate thereof, having the structure of Formula (IV):

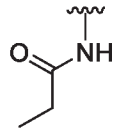


(IV)

wherein,

E is selected from a bond, $-SO_2-$, -C(O)-, $-CH_2-$, $-CH(R^4)-$, or $-C(R^4)_2-$;

G is:



;

wherein,

r is 0, 1, or 2;

each R^4 is independently selected from optionally substituted C1-C4 alkyl, or optionally substituted heterocyclylalkyl;

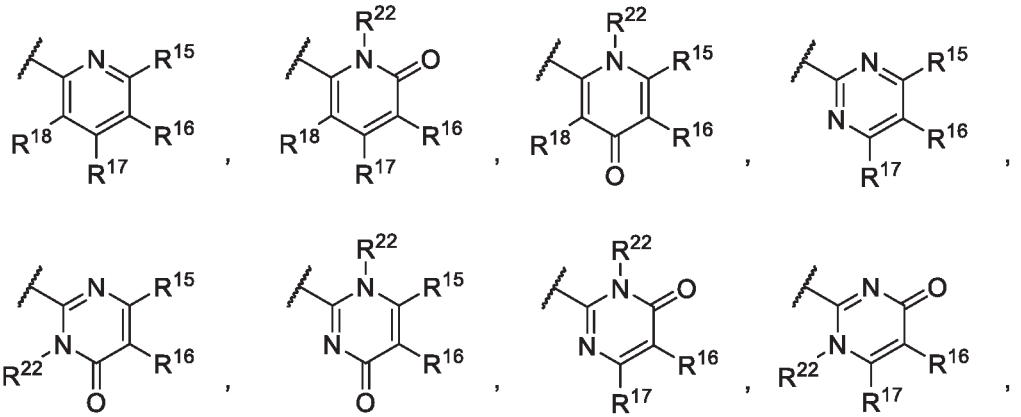
each R^{11} is independently hydrogen, halogen, optionally substituted C1-C6 alkyl, or both R^{11} groups form an oxo;

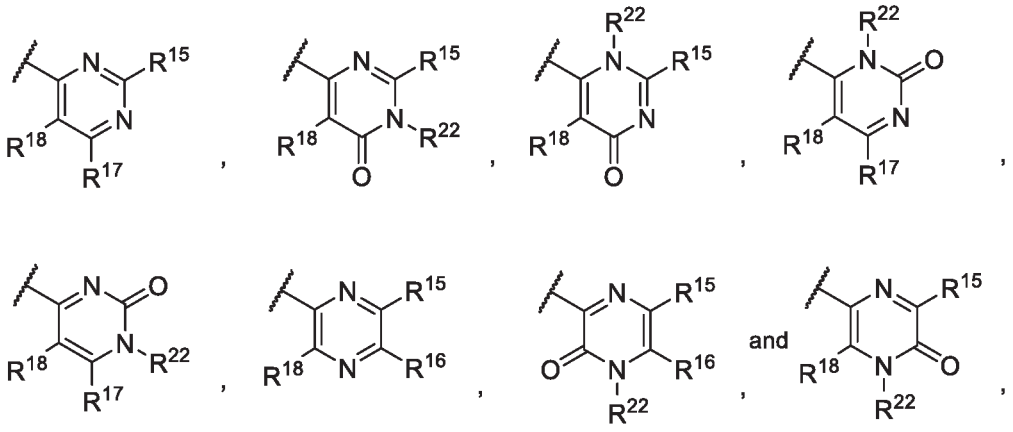
R^{12} is hydrogen or optionally substituted C1-C4 alkyl;

q is 0, 1, 2, or 3; n is 0, 1, 2, or 3; m is 0, 1, 2, or 3;

X is halogen, optionally substituted C1-C4 alkyl, optionally substituted C1-C4 alkoxy, optionally substituted cycloalkyl, optionally substituted heterocyclyl, optionally substituted aryl, or optionally substituted heteroaryl;

Y is a group selected from:





wherein,

R^{15} is selected from hydrogen, halogen, -CN, optionally substituted alkyl, optionally substituted alkoxy, optionally substituted cycloalkyl, optionally substituted heterocyclyl, optionally substituted cycloalkylalkyl, optionally substituted cycloalkyl-O-, optionally substituted aryl, optionally substituted aralkyl, optionally substituted heteroaryl, optionally substituted heteroaralkyl, optionally substituted aryloxy, optionally substituted aralkyloxy, optionally substituted heteroaryloxy, optionally substituted heteroaralkyloxy, $-N(R^{22})_2$, $-SO_2R^{21}$, $-N(R^{22})SO_2R^{21}$, $-SO_2N(R^{22})_2$, $-N(R^{22})SO_2N(R^{22})_2$, $-CON(R^{22})_2$, $-N(R^{22})CO_2R^{21}$, $-N(R^{22})CON(R^{22})_2$, $-N(R^{22})COR^{21}$, $-OC(O)N(R^{22})_2$, $-OSO_2N(R^{22})_2$, or $-N(R^{22})SO_3R^{21}$;

R^{16} is selected from hydrogen, halogen, -CN, optionally substituted alkyl, optionally substituted alkoxy, optionally substituted cycloalkyl, optionally substituted heterocyclyl, optionally substituted cycloalkylalkyl, optionally substituted cycloalkyl-O-, optionally substituted aryl, optionally substituted aralkyl, optionally substituted heteroaryl, optionally substituted heteroaralkyl, optionally substituted aryloxy, optionally substituted aralkyloxy, optionally substituted heteroaryloxy, optionally substituted heteroaralkyloxy, $-N(R^{22})_2$, $-SO_2R^{21}$, $-N(R^{22})SO_2R^{21}$, $-SO_2N(R^{22})_2$, $-N(R^{22})SO_2N(R^{22})_2$, $-CON(R^{22})_2$, $-N(R^{22})CO_2R^{21}$, $-N(R^{22})CON(R^{22})_2$, $-N(R^{22})COR^{21}$, $-OC(O)N(R^{22})_2$, $-OSO_2N(R^{22})_2$, or $-N(R^{22})SO_3R^{21}$;

R^{17} is selected from hydrogen, halogen, -CN, optionally substituted alkyl, optionally substituted alkoxy, optionally substituted cycloalkyl, optionally substituted heterocyclyl, optionally substituted cycloalkylalkyl, optionally substituted cycloalkyl-O-, optionally substituted aryl, optionally substituted aralkyl, optionally substituted heteroaryl, optionally substituted heteroaralkyl, optionally substituted aryloxy, optionally substituted aralkyloxy, optionally substituted heteroaryloxy, optionally substituted heteroaralkyloxy, $-N(R^{22})_2$, $-SO_2R^{21}$, $-N(R^{22})SO_2R^{21}$, $-SO_2N(R^{22})_2$, $-N(R^{22})SO_2N(R^{22})_2$, $-CON(R^{22})_2$, $-N(R^{22})CO_2R^{21}$, $-N(R^{22})CON(R^{22})_2$, $-N(R^{22})COR^{21}$, $-OC(O)N(R^{22})_2$, $-OSO_2N(R^{22})_2$, or $-N(R^{22})SO_3R^{21}$;

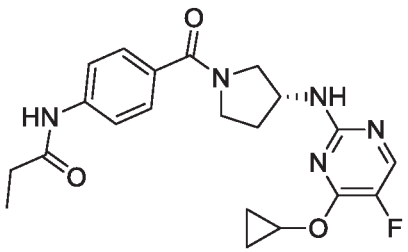
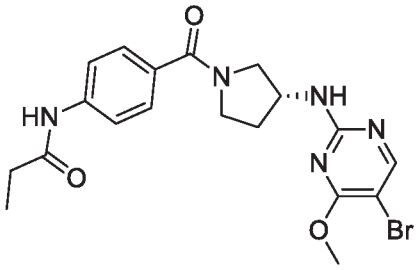
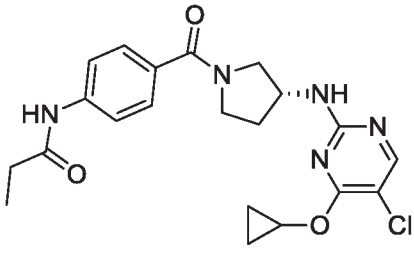
R^{18} is selected from hydrogen, halogen, -CN, optionally substituted alkyl, optionally substituted alkoxy, optionally substituted cycloalkyl, optionally substituted heterocyclyl, optionally substituted cycloalkylalkyl, optionally substituted cycloalkyl-O-, optionally substituted aryl, optionally substituted aralkyl, optionally substituted heteroaryl, optionally substituted heteroaralkyl, optionally substituted aryloxy, optionally substituted aralkyloxy, optionally substituted heteroaryloxy, optionally substituted heteroaralkyloxy, $-N(R^{22})_2$, $-SO_2R^{21}$, $-N(R^{22})SO_2R^{21}$, $-SO_2N(R^{22})_2$, $-N(R^{22})SO_2N(R^{22})_2$, $-CON(R^{22})_2$, $-N(R^{22})CO_2R^{21}$, $-N(R^{22})CON(R^{22})_2$, $-N(R^{22})COR^{21}$, $-OC(O)N(R^{22})_2$, $-OSO_2N(R^{22})_2$, or $-N(R^{22})SO_3R^{21}$;

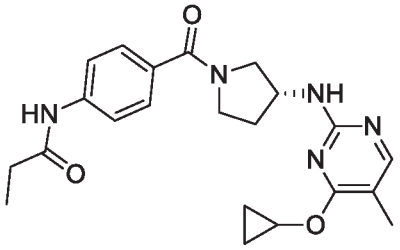
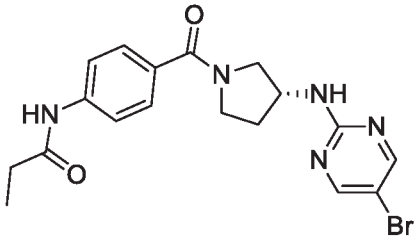
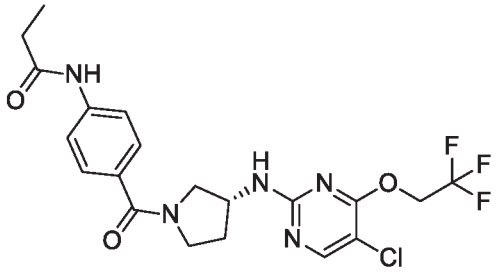
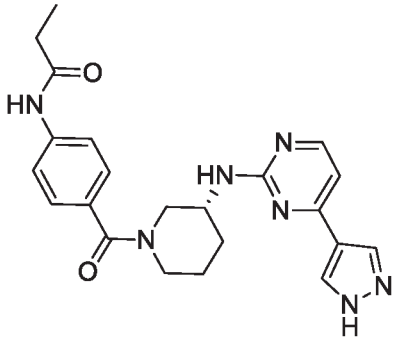
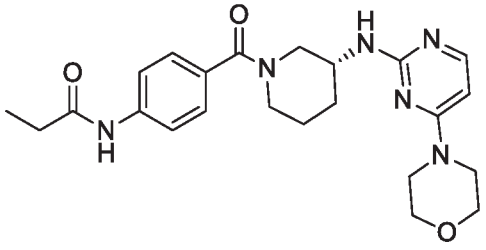
each R^{21} is independently selected from alkyl, cycloalkyl, cycloalkylalkyl, aryl, aralkyl, heterocyclyl, heterocyclylalkyl, heteroaryl, or heteroarylalkyl; and

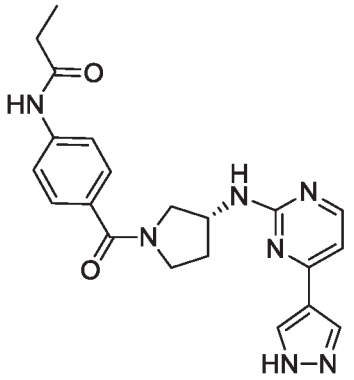
each R^{22} is independently selected from hydrogen, alkyl, cycloalkyl, cycloalkylalkyl, aryl, aralkyl, heterocyclyl, heterocyclylalkyl, heteroaryl, or heteroarylalkyl.

[00190] In some embodiments, the heteroaromatic CDK inhibitory compound of Formula (IV) as described herein has a structure provided in Table 3.

Table 3

Synthetic Chemistry Example	Compound Structure	Compound Name
13		(R)-N-(4-(3-((4-cyclopropoxy-5-fluoropyrimidin-2-yl)amino)pyrrolidine-1-carbonyl)phenyl)propionamide
14		(R)-N-(4-(3-((5-bromo-4-methoxypyrimidin-2-yl)amino)pyrrolidine-1-carbonyl)phenyl)propionamide
15		(R)-N-(4-(3-((5-chloro-4-cyclopropoxypyrimidin-2-yl)amino)pyrrolidine-1-carbonyl)phenyl)propionamide

Synthetic Chemistry Example	Compound Structure	Compound Name
16		(R)-N-(4-(3-((4-cyclopropoxy-5-methylpyrimidin-2-yl)amino)pyrrolidine-1-carbonyl)phenyl)propionamide
17		(R)-N-(4-(3-((5-bromopyrimidin-2-yl)amino)pyrrolidine-1-carbonyl)phenyl)propionamide
18		(R)-N-(4-(3-((5-chloro-4-(2,2,2-trifluoroethoxy)pyrimidin-2-yl)amino)pyrrolidine-1-carbonyl)phenyl)propionamide
41		(R)-N-(4-(3-((4-(1H-pyrazol-4-yl)pyrimidin-2-yl)amino)piperidine-1-carbonyl)phenyl)propionamide
42		(R)-N-(4-(3-((4-morpholinopyrimidin-2-yl)amino)piperidine-1-carbonyl)phenyl)propionamide

Synthetic Chemistry Example	Compound Structure	Compound Name
43		(R)-N-(4-(3-((4-(1H-pyrazol-4-yl)pyrimidin-2-yl)amino)pyrrolidine-1-carbonyl)phenyl)propionamide

Preparation of Compounds

[00191] The compounds used in the reactions described herein are made according to organic synthesis techniques known to those skilled in this art, starting from commercially available chemicals and/or from compounds described in the chemical literature. "Commercially available chemicals" are obtained from standard commercial sources including Acros Organics (Pittsburgh, PA), Aldrich Chemical (Milwaukee, WI, including Sigma Chemical and Fluka), Apin Chemicals Ltd. (Milton Park, UK), Avocado Research (Lancashire, U.K.), BDH Inc. (Toronto, Canada), Bionet (Cornwall, U.K.), Chemservice Inc. (West Chester, PA), Crescent Chemical Co. (Hauppauge, NY), Eastman Organic Chemicals, Eastman Kodak Company (Rochester, NY), Fisher Scientific Co. (Pittsburgh, PA), Fisons Chemicals (Leicestershire, UK), Frontier Scientific (Logan, UT), ICN Biomedicals, Inc. (Costa Mesa, CA), Key Organics (Cornwall, U.K.), Lancaster Synthesis (Windham, NH), Maybridge Chemical Co. Ltd. (Cornwall, U.K.), Parish Chemical Co. (Orem, UT), Pfaltz & Bauer, Inc. (Waterbury, CN), Polyorganix (Houston, TX), Pierce Chemical Co. (Rockford, IL), Riedel de Haen AG (Hanover, Germany), Spectrum Quality Product, Inc. (New Brunswick, NJ), TCI America (Portland, OR), Trans World Chemicals, Inc. (Rockville, MD), and Wako Chemicals USA, Inc. (Richmond, VA).

[00192] 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.,

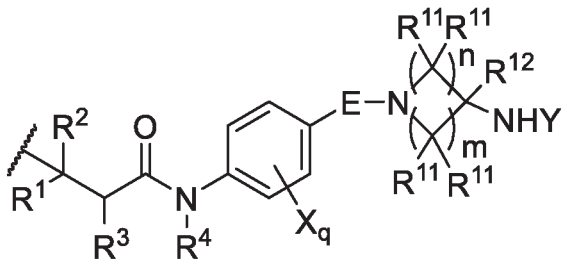
Wiley-Interscience, New York, 1992. Additional suitable reference books and treatise that detail the synthesis of reactants useful in the preparation of compounds described herein, or provide references to articles that describe the preparation, include for example, Fuhrhop, J. and Penzlin G. "Organic 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.

[00193] Specific and analogous reactants are optionally identified through the indices of known chemicals prepared by the Chemical Abstract Service of the American Chemical Society, which are available in most public and university libraries, as well as through on-line databases (contact the American Chemical Society, Washington, D.C. for more details). Chemicals that are known but not commercially available in catalogs are optionally prepared by custom chemical synthesis houses, where many of the standard chemical supply houses (*e.g.*, those listed above) provide custom synthesis services. A reference useful for the preparation and selection of pharmaceutical salts of the heteroaromatic CDK inhibitory compounds described herein is P. H. Stahl & C. G. Wermuth "Handbook of Pharmaceutical Salts", Verlag Helvetica Chimica Acta, Zurich, 2002.

Modification of Cyclin-Dependent Kinase

[00194] One embodiment provides a method of inhibiting a CDK enzyme comprising contacting the enzyme with a compound of Formula (I), (II), (III) or a compound disclosed in Table 1 or 2. One embodiment provides the method wherein the CDK enzyme is CDK12.

[00195] One embodiment provides a modified CDK12 polypeptide wherein the active site cysteine of an unmodified CDK12 has been modified with a substituent having the structure of Formula (V):



(V)

wherein,

E is selected from a bond, -SO_2-, -C(O)-, –CH_2-, -$CH(R^4)$-, or -$C(R^4)_2$-;

R^1 is selected from hydrogen, optionally substituted C1-C4 alkyl, or optionally substituted heterocyclylalkyl;

R^2 is selected from hydrogen, or optionally substituted C1-C4 alkyl;

R^3 is selected from hydrogen, -CN, or optionally substituted C1-C4 alkyl;

R^4 is selected from hydrogen, or optionally substituted C1-C4 alkyl;

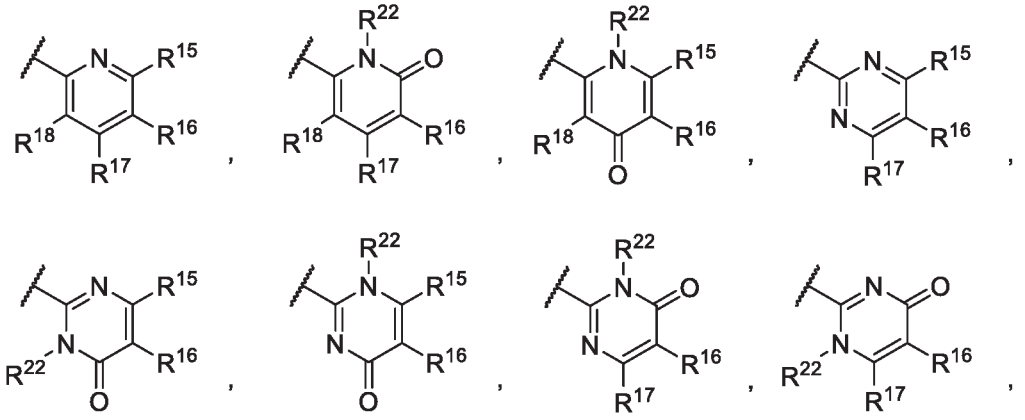
each R^{11} is independently hydrogen, halogen, optionally substituted C1-C6 alkyl, -OH, optionally substituted C1-C4 alkoxy, or two R^{11} groups on the same carbon atom form an oxo;

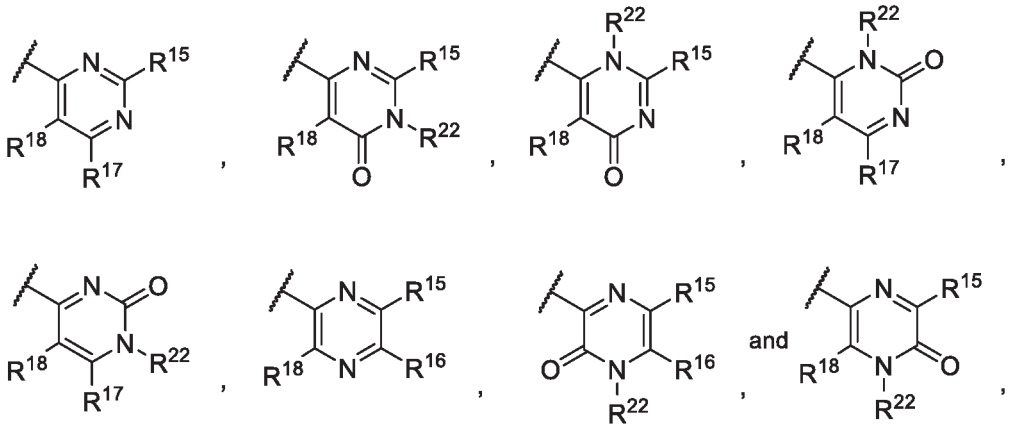
R^{12} is hydrogen or optionally substituted C1-C4 alkyl;

q is 0, 1, 2, or 3; n is 0, 1, 2, or 3; m is 0, 1, 2, or 3;

each X is independently halogen, optionally substituted C1-C4 alkyl, optionally substituted C1-C4 alkoxy, optionally substituted aminoalkyl, optionally substituted cycloalkyl, optionally substituted heterocyclyl, optionally substituted aryl, or optionally substituted heteroaryl;

Y is a group selected from:





wherein,

R^{15} is selected from hydrogen, halogen, -CN, optionally substituted alkyl, optionally substituted fluoroalkyl, optionally substituted alkoxy, optionally substituted cycloalkyl, optionally substituted heterocyclyl, optionally substituted cycloalkylalkyl, optionally substituted cycloalkyl-O-, optionally substituted aryl, optionally substituted aralkyl, optionally substituted aryloxy, optionally substituted aralkyloxy, optionally substituted heteroaryloxy, optionally substituted heteroaralkyloxy, $-OR^{22}$, $-N(R^{22})_2$, $-SO_2R^{21}$, $-N(R^{22})SO_2R^{21}$, $-SO_2N(R^{22})_2$, $-N(R^{22})SO_2N(R^{22})_2$, $-CON(R^{22})_2$, $-N(R^{22})CO_2R^{21}$, $-N(R^{22})CON(R^{22})_2$, $-N(R^{22})COR^{21}$, $-OC(O)N(R^{22})_2$, $-OSO_2N(R^{22})_2$, or $-N(R^{22})SO_3R^{21}$;

R^{16} is selected from hydrogen, halogen, -CN, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted fluoroalkyl, optionally substituted alkoxy, optionally substituted cycloalkyl, optionally substituted heterocyclyl, optionally substituted cycloalkylalkyl, optionally substituted cycloalkyl-O-, optionally substituted aryl, optionally substituted aralkyl, optionally substituted heteroaryl, optionally substituted heteroaralkyl, optionally substituted aryloxy, optionally substituted aralkyloxy, optionally substituted heteroaryloxy, optionally substituted heteroaralkyloxy, $-OR^{22}$, $-N(R^{22})_2$, $-SO_2R^{21}$, $-N(R^{22})SO_2R^{21}$, $-SO_2N(R^{22})_2$, $-N(R^{22})SO_2N(R^{22})_2$, $-CON(R^{22})_2$, $-N(R^{22})CO_2R^{21}$, $-N(R^{22})CON(R^{22})_2$, $-N(R^{22})COR^{21}$, $-OC(O)N(R^{22})_2$, $-OSO_2N(R^{22})_2$, or $-N(R^{22})SO_3R^{21}$;

R^{17} is selected from hydrogen, halogen, -CN, optionally substituted alkyl, optionally substituted fluoroalkyl, optionally substituted alkoxy, optionally substituted cycloalkyl, optionally substituted heterocyclyl, optionally substituted cycloalkylalkyl, optionally substituted cycloalkyl-O-, optionally substituted aryl, optionally substituted aralkyl, optionally substituted aryloxy, optionally substituted aralkyloxy, optionally substituted heteroaryloxy, optionally substituted heteroaralkyloxy, $-OR^{22}$, $-N(R^{22})_2$, $-SO_2R^{21}$, $-N(R^{22})SO_2R^{21}$, $-SO_2N(R^{22})_2$, $-N(R^{22})SO_2N(R^{22})_2$, $-CON(R^{22})_2$, $-N(R^{22})CO_2R^{21}$, $-N(R^{22})CON(R^{22})_2$, $-N(R^{22})COR^{21}$, $-OC(O)N(R^{22})_2$, $-OSO_2N(R^{22})_2$, or $-N(R^{22})SO_3R^{21}$;

each R^{21} is independently selected from alkyl, cycloalkyl, cycloalkylalkyl, aryl, aralkyl, heterocyclyl, heterocyclylalkyl, heteroaryl, or heteroarylalkyl; and

each R^{22} is independently selected from hydrogen, alkyl, cycloalkyl, cycloalkylalkyl, aryl, aralkyl, heterocyclyl, heterocyclylalkyl, heteroaryl, or heteroarylalkyl.

[00196] In some embodiments, q is 0, 1, or 2.

[00197] In some embodiments, q is 0, or 1.

[00198] In some embodiments, q is 0.

[00199] In some embodiments, X is a halogen. In some embodiments, X is an optionally substituted C1-C4 alkyl.

[00200] In some embodiments, R^2 is hydrogen.

[00201] In some embodiments, R^3 is hydrogen. In some embodiments, R^3 is hydrogen or –CN.

[00202] In some embodiments, R^2 and R^3 are hydrogen.

[00203] In some embodiments, R^1 is hydrogen. In some embodiments, R^1 is optionally substituted C1-C4 alkyl. In some embodiments, R^1 is optionally substituted C1-C2 alkyl. In some embodiments, R^1 is optionally substituted C1 alkyl. In some embodiments, the C1 alkyl is substituted with an optionally substituted amino group. In some embodiments, the optionally substituted amino group is a dimethylamino.

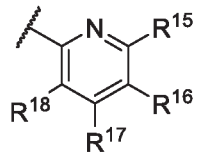
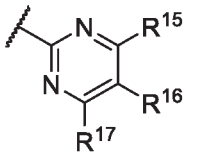
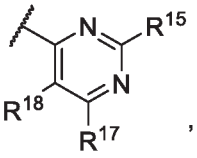
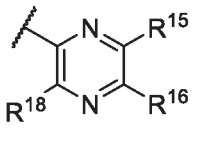
[00204] In some embodiments, R^1 is $–CH_2\text{-}N(Me)_2$.

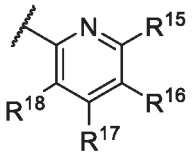
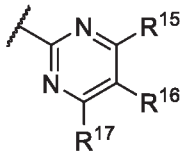
[00205] In some embodiments, R^1 is optionally substituted heterocyclylalkyl. In some embodiments, the optionally substituted heterocyclylalkyl comprises an optionally substituted C1 alkyl. In some embodiments, the optionally substituted heterocyclylalkyl comprises an optionally substituted N-linked heterocyclyl. In some embodiments, the optionally substituted N-linked heterocyclyl is an N-linked pyrrolidine or piperidine.

[00206] In some embodiments, R^4 is hydrogen. In some embodiments, R^4 is optionally substituted C1-C4 alkyl. In some embodiments, R^4 is CH_3.

[00207] In some embodiments, n is 1 and m is 1. In some embodiments, n is 1 and m is 2. In some embodiments, n is 1 and m is 3.

[00208] In some embodiments, Y is selected from:


, 
, 
, or 
.

[00209] In some embodiments, Y is:  . In some embodiments, Y is:  .

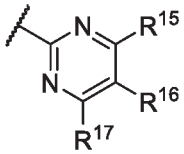
[00210] In some embodiments, R^{15} is selected from hydrogen, halogen, -CN, and optionally substituted alkyl. In some embodiments, R^{15} is hydrogen.

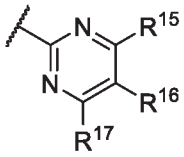
[00211] In some embodiments, R^{16} is selected from hydrogen, halogen, -CN, optionally substituted alkyl, optionally substituted fluoroalkyl, optionally substituted alkoxy, optionally substituted cycloalkyl, optionally substituted heterocyclyl, optionally substituted cycloalkylalkyl, optionally substituted cycloalkyl-O-, optionally substituted aryl, optionally substituted aralkyl, optionally substituted heteroaryl, optionally substituted heteroaralkyl, optionally substituted aryloxy, optionally substituted aralkyloxy, optionally substituted heteroaryloxy, optionally substituted heteroaralkyloxy, $-OR^{22}$, $-N(R^{22})_2$, $-SO_2R^{21}$, $-N(R^{22})SO_2R^{21}$, $-SO_2N(R^{22})_2$, $-N(R^{22})SO_2N(R^{22})_2$, $-CON(R^{22})_2$, $-N(R^{22})CO_2R^{21}$, $-N(R^{22})CON(R^{22})_2$, $-N(R^{22})COR^{21}$, $-OC(O)N(R^{22})_2$, $-OSO_2N(R^{22})_2$, or $-N(R^{22})SO_3R^{21}$.

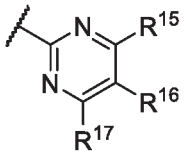
[00212] In some embodiments, L is O, NH, or N(optionally substituted C1-C4 alkyl); and R^{16} is selected from hydrogen, halogen, -CN, optionally substituted alkyl, optionally substituted fluoroalkyl, optionally substituted alkoxy, optionally substituted cycloalkyl, optionally substituted heterocyclyl, optionally substituted cycloalkylalkyl, optionally substituted cycloalkyl-O-, optionally substituted aryl, optionally substituted aralkyl, optionally substituted heteroaryl, optionally substituted heteroaralkyl, optionally substituted aryloxy, optionally substituted aralkyloxy, optionally substituted heteroaryloxy, optionally substituted heteroaralkyloxy, $-OR^{22}$, $-N(R^{22})_2$, $-SO_2R^{21}$, $-N(R^{22})SO_2R^{21}$, $-SO_2N(R^{22})_2$, $-N(R^{22})SO_2N(R^{22})_2$, $-CON(R^{22})_2$, $-N(R^{22})CO_2R^{21}$, $-N(R^{22})CON(R^{22})_2$, $-N(R^{22})COR^{21}$, $-OC(O)N(R^{22})_2$, $-OSO_2N(R^{22})_2$, or $-N(R^{22})SO_3R^{21}$.

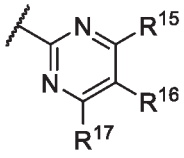
[00213] In some embodiments, R^{16} is selected from hydrogen, halogen, -CN, and optionally substituted alkyl. In some embodiments, R^{16} is hydrogen.

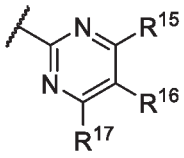
[00214] In some embodiments, R^{16} is selected from optionally substituted alkyl, optionally substituted alkenyl, or optionally substituted alkynyl. In some embodiments, R^{16} is selected from optionally substituted alkynyl.

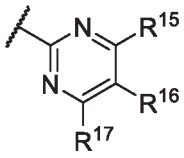
[00215] In some embodiments, Y is:  , and R^{16} is not hydrogen.

[00216] In some embodiments, Y is: , and R^{16} is halogen.

[00217] In some embodiments, Y is: , and R^{16} is selected from optionally substituted alkyl, optionally substituted alkenyl, or optionally substituted alkynyl.

[00218] In some embodiments, Y is: , R^{15} is hydrogen, R^{16} is selected from optionally substituted alkynyl, and R^{17} is hydrogen or optionally substituted alkoxy.

[00219] In some embodiments, Y is: ; R^{15} is hydrogen, R^{16} is selected from halogen, -CN, optionally substituted alkyl, optionally substituted fluoroalkyl, optionally substituted alkenyl, optionally substituted alkynyl, and R^{17} is hydrogen or optionally substituted alkoxy.

[00220] In some embodiments, n is 1 and m is 2; Y is: ; R^{15} is hydrogen, R^{16} is selected from halogen, -CN, optionally substituted alkyl, optionally substituted fluoroalkyl, optionally substituted alkenyl, optionally substituted alkynyl, and R^{17} is hydrogen or optionally substituted alkoxy.

[00221] In some embodiments, R^{17} is selected from hydrogen, halogen, -CN, and optionally substituted alkyl. In some embodiments, R^{17} is hydrogen.

[00222] In some embodiments, R^{18} is selected from hydrogen, halogen, -CN, and optionally substituted alkyl. In some embodiments, R^{18} is hydrogen.

[00223] In some embodiments, R^{15} and R^{16} are hydrogen. In some embodiments, R^{17} and R^{18} are hydrogen.

[00224] In some embodiments, R^{15} and R^{17} are hydrogen.

In some embodiments, E is a bond. In some embodiments, E is $-SO_2-$. In some embodiments, E is -C(O)-. In some embodiments, E is $–CH_2-$. In some embodiments, E is $-CH(R^4)-$. In some embodiments, E is $-C(R^4)_2-$.

[00225] Another embodiment provides the modified CDK12 polypeptide wherein the unmodified CDK12 polypeptide is isoform 1 (homo sapiens).

[00226] Another embodiment provides the modified CDK12 polypeptide wherein the unmodified CDK12 polypeptide is isoform 2 (homo sapiens).

[00227] Another embodiment provides the modified CDK12 polypeptide wherein the unmodified CDK12 polypeptide is an isoform 1 (homo sapiens) variant. Another embodiment provides the modified CDK12 polypeptide wherein the unmodified CDK12 polypeptide is isoform 1 (homo sapiens) variant I1131V. Another embodiment provides the modified CDK12 polypeptide wherein the unmodified CDK12 polypeptide is isoform 1 (homo sapiens) variant L1189Q. Another embodiment provides the modified CDK12 polypeptide wherein the unmodified CDK12 polypeptide is isoform 1 (homo sapiens) variant T1195M.

[00228] Another embodiment provides the modified CDK12 polypeptide wherein the unmodified CDK12 polypeptide is a SEQID selected from a SEQID provided in Table 4 or 5.

Table 4. CDK12 Sequences

SEQ ID NO	Ensembl Protein ID (Accession Number)	Amino Acid Sequence
1	ENSP00000398880 (NP_057591.2)	MPNSERHGGKKDGSGGASGTLQPSSGGGSSNSRERHRLVSKHKRHK SKHSKDMGLVTPEAASLGTVIKPLVEYDDISSDSDTFSDDMAFKLDR RENDERRGSDRSDRLHKHRHHQHRRSRDLLKAKQTEKEKSQEVSSK SGSMKDRISGSSKRSNEETDDYGKAQVAKSSSKESRSSKLHKEKTRK ERELKSGHKDRSKSHRKRETPKSYKTVDSPKRRSRSPHRKWSDSSKQ DDSPSGASYGQDYDLSPSRSHTSSNYDSYKKSPGSTSRRQSVSPPYKE PSAYQSSTRSPSPYSRRQRSVSPYSRRRSSSYERSGSYSGRSPSPYGRR RSSSPFLSKRSLSRSPLPSRKSMKSRSRSPAYSRHSSSHSKKKRSSSRS RHSSISPVRLPLNSSLGAELSRKKKERAAAAAAAKMDGKESKGSPVF LPRKENSSVEAKDSGLESKKLPRSVKLEKSAPDTELVNVTHLNTEVK NSSDTGKVKLDENSEKHLVKDLKAQGTRDSKPIALKEEIVTPKETETS EKETPPPLPTIASPPPPLPTTTPPPQTPPLPPLPPIPALPQQPPLPPSQPAF SQVPASSTSTLPPSTHSKTSAVSSQANSQPPVQVSVKTQVSVTAAIPH LKTSTLPPLPLPPLLPGDDDMDSPKETLPSKPVKKEKEQRTRHLLTDL PLPPELPGGDLSPPDSPEPKAITPPQQPYKKRPKICCPRYGERRQTESD WGKRCVDKFDIIGIIGEGTYGQVYKAKDKDTGELVALKKVRLDNEK EGFPITAIREIKILRQLIHRSVVNMKEIVTDKQDALDFKKDKGAFYLV

		FEYMDHDLMGLLESGLVHFSEDHIKSFMKQLMEGLEYCHKKNFLHR DIKCSNILLNNSGQIKLADFGLARLYNSEESRPYTNKVITLWYRPPEL LLGEERYTPAIDVWSCGCILGELFTKKPIFQANLELAQLELISRLCGSP CPAVWPDVIKLPYFNTMKPKKQYRRRLREEFSFIPSAALDLLDHMLT LDPSKRCTAEQTLQSDFLKDVELSKMAPPDLPHWQDCHELWSKKRR RQRQSGVVVEEPPPSKTSRKETTSGTSTEPVKNSSPAPPQPAPGKVES GAGDAIGLADITQQLNQSELAVLLNLLQSQTDLSIPQMAQLLNIHSNP EMQQQLEALNQSISALTEATSQQQDSETMAPEESLKEAPSAPVILPSA EQTTLEASSTPADMQNILAVLLSQLMKTQEPAGSLEENNSDKNSGPQ GPRRTPTMPQEEAAACPPHILPPEKRPPEPPGPPPPPPPPLVEGDLSSA PQELNPAVTAALLQLLSQPEAEPPGHLPHEHQALRPMEYSTRPRPNR TYGNTDGPETGFSAIDTDERNSGPALTESLVQTLVKNRTFSGSLSHLG ESSSYQGTGSVQFPGDQDLRFARVPLALHPVVGQPFLKAEGSSNSVV HAETKLQNYGELGPGTTGASSSGAGLHWGGPTQSSAYGKLYRGPTR VPPRGGRGRGVPY
2	ENSP0000 0407720 (NP_05589 8.1)	MPNSERHGGKKDGSGGASGTLQPSSGGGSSNSRERHRLVSKHKRHK SKHSKDMGLVTPEAASLGTVIKPLVEYDDISSDSDTFSDDMAFKLDR RENDERRGSDRSDRLHKHRHHQHRRSRDLLKAKQTEKEKSQEVSSK SGSMKDRISGSSKRSNEETDDYGKAQVAKSSSKESRSSKLHKEKTRK ERELKSGHKDRSKSHRKRETPKSYKTVDSPKRRSRSPHRKWSDSSKQ DDSPSGASYGQDYDLSPSRSHTSSNYDSYKKSPGSTSRRQSVSPPYKE PSAYQSSTRSPSPYSRRQRSVSPYSRRRSSSYERSGSYSGRSPSPYGRR RSSSPFLSKRSLSRSPLPSRKSMKSRSRSPAYSRHSSSHSKKKRSSSRS RHSSISPVRLPLNSSLGAELSRKKKERAAAAAAAKMDGKESKGSPVF LPRKENSSVEAKDSGLESKKLPRSVKLEKSAPDTELVNVTHLNTEVK NSSDTGKVKLDENSEKHLVKDLKAQGTRDSKPIALKEEIVTPKETETS EKETPPPLPTIASPPPPLPTTTPPPQTPPLPPLPPIPALPQQPPLPPSQPAF SQVPASSTSTLPPSTHSKTSAVSSQANSQPPVQVSVKTQVSVTAAIPH LKTSTLPPLPLPPLLPGDDDMDSPKETLPSKPVKKEKEQRTRHLLTDL PLPPELPGGDLSPPDSPEPKAITPPQQPYKKRPKICCPRYGERRQTESD WGKRCVDKFDIIGIIGEGTYGQVYKAKDKDTGELVALKKVRLDNEK EGFPITAIREIKILRQLIHRSVVNMKEIVTDKQDALDFKKDKGAFYLV FEYMDHDLMGLLESGLVHFSEDHIKSFMKQLMEGLEYCHKKNFLHR

		DIKCSNILLNNSGQIKLADFGLARLYNSEESRPYTNKVITLWYRPPEL LLGEERYTPAIDVWSCGCILGELFTKKPIFQANLELAQLELISRLCGSP CPAVWPDVIKLPYFNTMKPKKQYRRRLREEFSFIPSAALDLLDHMLT LDPSKRCTAEQTLQSDFLKDVELSKMAPPDLPHWQDCHELWSKKRR RQRQSGVVVEEPPPSKTSRKETTSGTSTEPVKNSSPAPPQPAPGKVES GAGDAIGLADITQQLNQSELAVLLNLLQSQTDLSIPQMAQLLNIHSNP EMQQQLEALNQSISALTEATSQQQDSETMAPEESLKEAPSAPVILPSA EQTTLEASSTPADMQNILAVLLSQLMKTQEPAGSLEENNSDKNSGPQ GPRRTPTMPQEEAAEKRPPEPPGPPPPPPPPLVEGDLSSAPQELNPAV TAALLQLLSQPEAEPPGHLPHEHQALRPMEYSTRPRPNRTYGNTDGP ETGFSAIDTDERNSGPALTESLVQTLVKNRTFSGSLSHLGESSSYQGT GSVQFPGDQDLRFARVPLALHPVVGQPFLKAEGSSNSVVHAETKLQ NYGELGPGTTGASSSGAGLHWGGPTQSSAYGKLYRGPTRVPPRGGR GRGVPY
3	ENSP0000 0464641	MPNSERHGGKKDGSGGASGTLQPSSGGGSSNSRERHRLVSKHKRHK SKHSKDMGLVTPEAASLGTVIKPLVEYDDISSDSDTFSDDMAFKLDR RENDERRGSDRSDRLHKHRHHQHRRSRDLLKAKQTEKEKSQEVSSK SGSMKDRISGSSKRSNEETDDYGKAQVAKSSSKESRSSKLHKEKTRK ERELKSGHKDRSKSHRKRETPKSYKTVDSPKRRSRSPHRKWSDSSKQ DDSPSGASYGQDYDLSPSRSHTSSNYDSYKKSPGSTSRRQSVSPPYKE PSAYQSSTRSPSPYSRRQRSVSPYSRRRSSSYERSGSYSGRSPSPYGRR RSSSPFLSKRSLSRSPLPRKSMKSRSRSPAYSRHSSSHSKKKRSSSRSR HSSISPVRLPLNSSLGAELSRKKKERAAAAAAAKMDGKESKGSPVFL PRKENSSVEAKDSGLESKKLPRSVKLEKSAPDTELVNVTHLNTEVKN SSDTGKVKLDENSEKHLVKDLKAQGTRDSKPIALKEEIVTPKETETSE KETPPPLPTIASPPPPLPTTTPPPQTPPLPPLPPIPALPQQPPLPPSQPAFS QVPASSTSTLPPSTHSKTSAVSSQANSQPPVQVSVKTQVSVTAAIPHL KTSTLPPLPLPPLLPGDDDMDSPKETLPSKPVKKEKEQRTRHLLTDLP LPPELPGGDLSPPDSPEPKAITPPQQPYKKRPKICCPRYGERRQTESDW GKRCVDKFDIIGIIGEGTYGQVYKAKDKDTGELVALKKVRLDNEKE GFPITAIREIKILRQLIHRSVVNMKEIVTDKQDALDFKKDKGAFYLVF EYMDHDLMGLLESGLVHFSEDHIKSFMKQLMEGLEYCHKKNFLHR DIKCSNILLNNSGQIKLADFGLARLYNSEESRPYTNKVITLWYRPPEL

		LLGEERYTPAIDVWSCGCILGELFTKKPIFQANLELAQLELISRLCGSP CPAVWPDVIKLPYFNTMKPKKQYRRRLREEFSFIPSAALDLLDHMLT LDPSKRCTAEQTLQSDFLKDVELSKMAPPDLPHWQDCHELWSKKRR RQRQSGVVVEEPPPSKTSRKETTSGTSTEPVKNSSPAPPQPAPGKVES GAGDAIGLADITQQLNQSELAVLLNLLQSQTDLSIPQMAQLLNIHSNP EMQQQLEALNQSISALTEATSQQQDSETMAPEESLKEAPSAPVILPSA EQTTLEASST
4	ENSP0000 0453329	XADITQQLNQSELAVLLNLLQSQTDLSIPQMAQLLNIHSNPEMQQQL EALNQSISALTEATSQQQDSETMAPEESLKEAPSAPVILPSAEQTTLEA SSTPADMQNILAVLLSQLMKTQEPAGSLEENNSDKNSGPQGPRRTPT MPQEEAAGRSNGGNAL

Table 5. Variant CDK12 Sequences

SEQ ID NO	Amino Acid Sequence
5	MPNSERHGGKKDGSGGASGTLQPSSGGGSSNSRERHRLVSKHKRHKSKHSKDMG LVTPEAASLGTVIKPLVEYDDISSDSDTFSDDMAFKLDRRENDERRGSDRSDRLHK HRHHQHRRSRDLLKAKQTEKEKSQEVSSKSGSMKDRISGSSKRSNEETDDYGKAQ VAKSSSKESRSSKLHKEKTRKERELKSGHKDRSKSHRKRETPKSYKTVDSPKRRSR SPHRKWSDSSKQDDSPSGASYGQDYDLSPSRSHTSSNYDSYKKSPGSTSRRQSVSP PYKEPSAYQSSTRSPSPYSRRQRSVSPYSRRRSSSYERSGSYSGRSPSPYGRRRSSSP FLSKRSLSRSPLPSRKSMKSRSRSPAYSRHSSSHSKKKRSSSRSRHSSISPVRLPLNSS LGAELSRKKKERAAAAAAAKMDGKESKGSPVFLPRKENSSVEAKDSGLESKKLP RSVKLEKSAPDTELVNVTHLNTEVKNSSDTGKVKLDENSEKHLVKDLKAQGTRD SKPIALKEEIVTPKETETSEKETPPPLPTIASPPPPLPTTTPPPQTPPLPPLPPIPALPQQP PLPPSQPAFSQVPASSTSTLPPSTHSKTSAVSSQANSQPPVQVSVKTQVSVTAAIPHL KTSTLPPLPLPPLLPGDDDMDSPKETLPSKPVKKEKEQRTRHLLTDLPLPPELPGGD LSPPDSPEPKAITPPQQPYKKRPKICCPRYGERRQTESDWGKRCVDKFDIIGIIGEGT YGQVYKAKDKDTGELVALKKVRLDNEKEGFPITAIREIKILRQLIHRSVVNMKEIV TDKQDALDFKKDKGAFYLVFEYMDHDLMGLLESGLVHFSEDHIKSFMKQLMEGL EYCHKKNFLHRDIKCSNILLNNSGQIKLADFGLARLYNSEESRPYTNKVITLWYRP PELLLGEERYTPAIDVWSCGCILGELFTKKPIFQANLELAQLELISRLCGSPCPAVW PDVIKLPYFNTMKPKKQYRRRLREEFSFIPSAALDLLDHMLTLDPSKRCTAEQTLQ

	SDFLKDVELSKMAPPDLPHWQDCHELWSKKRRRQRQSGVVVEEPPPSKTSRKETT SGTSTEPVKNSSPAPPQPAPGKVESGAGDAIGLADITQQLNQSELAVLLNLLQSQT DLS**V**PQMAQLLNIHSNPEMQQQLEALNQSISALTEATSQQQDSETMAPEESLKEAP SAPVILPSAEQTTLEASSTPADMQNILAVLLSQLMKTQEPAGSLEENNSDKNSGPQ GPRRTPTMPQEEAAACPPHILPPEKRPPEPPGPPPPPPPPPLVEGDLSSAPQELNPAV TAALLQLLSQPEAEPPGHLPHEHQALRPMEYSTRPRPNRTYGNTDGPETGFSAIDT DERNSGPALTESLVQTLVKNRTFSGSLSHLGESSSYQGTGSVQFPGDQDLRFARVP LALHPVVGQPFLKAEGSSNSVVHAETKLQNYGELGPGTTGASSSGAGLHWGGPT QSSAYGKLYRGPTRVPPRGGRGRGVPY
6	MPNSERHGGKKDGSGGASGTLQPSSGGGSSNSRERHRLVSKHKRHKSKHSKDMG LVTPEAASLGTVIKPLVEYDDISSDSDTFSDDMAFKLDRRENDERRGSDRSDRLHK HRHHQHRRSRDLLKAKQTEKEKSQEVSSKSGSMKDRISGSSKRSNEETDDYGKAQ VAKSSSKESRSSKLHKEKTRKERELKSGHKDRSKSHRKRETPKSYKTVDSPKRRSR SPHRKWSDSSKQDDSPSGASYGQDYDLSPSRSHTSSNYDSYKKSPGSTSRRQSVSP PYKEPSAYQSSTRSPSPYSRRQRSVSPYSRRRSSSYERSGSYSGRSPSPYGRRRSSSP FLSKRSLSRSPLPSRKSMKSRSRSPAYSRHSSSHSKKKRSSSRSRHSSISPVRLPLNSS LGAELSRKKKERAAAAAAAKMDGKESKGSPVFLPRKENSSVEAKDSGLESKKLP RSVKLEKSAPDTELVNVTHLNTEVKNSSDTGKVKLDENSEKHLVKDLKAQGTRD SKPIALKEEIVTPKETETSEKETPPPLPTIASPPPPLPTTTPPPQTPPLPPLPPIPALPQQP PLPPSQPAFSQVPASSTSTLPPSTHSKTSAVSSQANSQPPVQVSVKTQVSVTAAIPHL KTSTLPPLPLPPLLPGDDDMDSPKETLPSKPVKKEKEQRTRHLLTDLPLPPELPGGD LSPPDSPEPKAITPPQQPYKKRPKICCPRYGERRQTESDWGKRCVDKFDIIGIIGEGT YGQVYKAKDKDTGELVALKKVRLDNEKEGFPITAIREIKILRQLIHRSVVNMKEIV TDKQDALDFKKDKGAFYLVFEYMDHDLMGLLESGLVHFSEDHIKSFMKQLMEGL EYCHKKNFLHRDIKCSNILLNNSGQIKLADFGLARLYNSEESRPYTNKVITLWYRP PELLLGEERYTPAIDVWSCGCILGELFTKKPIFQANLELAQLELISRLCGSPCPAVW PDVIKLPYFNTMKPKKQYRRRLREEFSFIPSAALDLLDHMLTLDPSKRCTAEQTLQ SDFLKDVELSKMAPPDLPHWQDCHELWSKKRRRQRQSGVVVEEPPPSKTSRKETT SGTSTEPVKNSSPAPPQPAPGKVESGAGDAIGLADITQQLNQSELAVLLNLLQSQT DLSIPQMAQLLNIHSNPEMQQQLEALNQSISALTEATSQQQDSETMAPEESLKEAP SAPVI**Q**PSAEQTTLEASSTPADMQNILAVLLSQLMKTQEPAGSLEENNSDKNSGPQ GPRRTPTMPQEEAAACPPHILPPEKRPPEPPGPPPPPPPPPLVEGDLSSAPQELNPAV TAALLQLLSQPEAEPPGHLPHEHQALRPMEYSTRPRPNRTYGNTDGPETGFSAIDT

	DERNSGPALTESLVQTLVKNRTFSGSLSHLGESSSYQGTGSVQFPGDQDLRFARVP LALHPVVGQPFLKAEGSSNSVVHAETKLQNYGELGPGTTGASSSGAGLHWGGPT QSSAYGKLYRGPTRVPPRGGRGRGVPY
7	MPNSERHGGKKDGSGGASGTLQPSSGGGSSNSRERHRLVSKHKRHKSKHSKDMG LVTPEAASLGTVIKPLVEYDDISSDSDTFSDDMAFKLDRRENDERRGSDRSDRLHK HRHHQHRRSRDLLKAKQTEKEKSQEVSSKSGSMKDRISGSSKRSNEETDDYGKAQ VAKSSSKESRSSKLHKEKTRKERELKSGHKDRSKSHRKRETPKSYKTVDSPKRRSR SPHRKWSDSSKQDDSPSGASYGQDYDLSPSRSHTSSNYDSYKKSPGSTSRRQSVSP PYKEPSAYQSSTRSPSPYSRRQRSVSPYSRRRSSSYERSGSYSGRSPSPYGRRRSSSP FLSKRSLSRSPLPSRKSMKSRSRSPAYSRHSSSHSKKKRSSSRSRHSSISPVRLPLNSS LGAELSRKKKERAAAAAAAKMDGKESKGSPVFLPRKENSSVEAKDSGLESKKLP RSVKLEKSAPDTELVNVTHLNTEVKNSSDTGKVKLDENSEKHLVKDLKAQGTRD SKPIALKEEIVTPKETETSEKETPPPLPTIASPPPPLPTTTPPPQTPPLPPLPPIPALPQQP PLPPSQPAFSQVPASSTSTLPPSTHSKTSAVSSQANSQPPVQVSVKTQVSVTAAIPHL KTSTLPPLPLPPLLPGDDDMDSPKETLPSKPVKKEKEQRTRHLLTDLPLPPELPGGD LSPPDSPEPKAITPPQQPYKKRPKICCPRYGERRQTESDWGKRCVDKFDIIGIIGEGT YGQVYKAKDKDTGELVALKKVRLDNEKEGFPITAIREIKILRQLIHRSVVNMKEIV TDKQDALDFKKDKGAFYLVFEYMDHDLMGLLESGLVHFSEDHIKSFMKQLMEGL EYCHKKNFLHRDIKCSNILLNNSGQIKLADFGLARLYNSEESRPYTNKVITLWYRP PELLLGEERYTPAIDVWSCGCILGELFTKKPIFQANLELAQLELISRLCGSPCPAVW PDVIKLPYFNTMKPKKQYRRRLREEFSFIPSAALDLLDHMLTLDPSKRCTAEQTLQ SDFLKDVELSKMAPPDLPHWQDCHELWSKKRRRQRQSGVVVEEPPPSKTSRKETT SGTSTEPVKNSSPAPPQPAPGKVESGAGDAIGLADITQQLNQSELAVLLNLLQSQT DLSIPQMAQLLNIHSNPEMQQQLEALNQSISALTEATSQQQDSETMAPEESLKEAP SAPVILPSAEQ**M**TLEASSTPADMQNILAVLLSQLMKTQEPAGSLEENNSDKNSGPQ GPRRTPTMPQEEAAACPPHILPPEKRPPEPPGPPPPPPPPPLVEGDLSSAPQELNPAV TAALLQLLSQPEAEPPGHLPHEHQALRPMEYSTRPRPNRTYGNTDGPETGFSAIDT DERNSGPALTESLVQTLVKNRTFSGSLSHLGESSSYQGTGSVQFPGDQDLRFARVP LALHPVVGQPFLKAEGSSNSVVHAETKLQNYGELGPGTTGASSSGAGLHWGGPT QSSAYGKLYRGPTRVPPRGGRGRGVPY
8	MPNSERHGGKKDGSGGASGTLQPSSGGGSSNSRERHRLVSKHKRHKSKHSKDMG LVTPEAASLGTVIKPLVEYDDISSDSDTFSDDMAFKLDRRENDERRGSDRSDRLHK HRHHQHRRSRDLLKAKQTEKEKSQEVSSKSGSMKDRISGSSKRSNEETDDYGKAQ

	VAKSSSKESRSSKLHKEKTRKERELKSGHKDRSKSHRKRETPKSYKTVDSPKRRSR SPHRKWSDSSKQDDSPSGASYGQDYDLSPSRSHTSSNYDSYKKSPGSTSRRQSVSP PYKEPSAYQSSTRSPSPYSRRQRSVSPYSRRRSSSYERSGSYSGRSPSPYGRRRSSSP FLSKRSLSRSPLPSRKSMKSRSRSPAYSRHSSSHSKKKRSSSRSRHSSISPVRLPLNSS LGAELSRKKKERAAAAAAAKMDGKESKGSPVFLPRKENSSVEAKDSGLESKKLP RSVKLEKSAPDTELVNVTHLNTEVKNSSDTGKVKLDENSEKHLVKDLKAQGTRD SKPIALKEEIVTPKETETSEKETPPPLPTIASPPPPLPTTTPPPQTPPLPPLPPIPALPQQP PLPPSQPAFSQVPASSTSTLPPSTHSKTSAVSSQANSQPPVQVSVKTQVSVTAAIPHL KTSTLPPLPLPPLLPGDDDMDSPKETLPSKPVKKEKEQRTRHLLTDLPLPPELPGGD LSPPDSPEPKAITPPQQPYKKRPKICCPRYGERRQTESDWGKRCVDKFDIIGIIGEGT YGQVYKAKDKDTGELVALKKVRLDNEKEGFPITAIREIKILRQLIHRSVVNMKEIV TDKQDALDFKKDKGAFYLVFEYMDHDLMGLLESGLVHFSEDHIKSFMKQLMEGL EYCHKKNFLHRDIKCSNILLNNSGQIKLADFGLARLYNSEESRPYTNKVITLWYRP PELLLGEERYTPAIDVWSCGCILGELFTKKPIFQANLELAQLELISRLCGSPCPAVW PDVIKLPYFNTMKPKKQYRRRLREEFSFIPSAALDLLDHMLTLDPSKRCTAEQTLQ SDFLKDVELSKMAPPDLPHWQDCHELWSKKRRRQRQSGVVVEEPPPSKTSRKETT SGTSTEPVKNSSPAPPQPAPGKVESGAGDAIGLADITQQLNQSELAVLLNLLQSQT DLSVPQMAQLLNIHSNPEMQQQLEALNQSISALTEATSQQQDSETMAPEESLKEAP SAPVILPSAEQTTLEASSTPADMQNILAVLLSQLMKTQEPAGSLEENNSDKNSGPQ GPRRTPTMPQEEAAEKRPPEPPGPPPPPPPPLVEGDLSSAPQELNPAVTAALLQLL SQPEAEPPGHLPHEHQALRPMEYSTRPRPNRTYGNTDGPETGFSAIDTDERNSGPA LTESLVQTLVKNRTFSGSLSHLGESSSYQGTGSVQFPGDQDLRFARVPLALHPVVG QPFLKAEGSSNSVVHAETKLQNYGELGPGTTGASSSGAGLHWGGPTQSSAYGKL YRGPTRVPPRGGRGRGVPY
9	MPNSERHGGKKDGSGGASGTLQPSSGGGSSNSRERHRLVSKHKRHKSKHSKDMG LVTPEAASLGTVIKPLVEYDDISSDSDTFSDDMAFKLDRRENDERRGSDRSDRLHK HRHHQHRRSRDLLKAKQTEKEKSQEVSSKSGSMKDRISGSSKRSNEETDDYGKAQ VAKSSSKESRSSKLHKEKTRKERELKSGHKDRSKSHRKRETPKSYKTVDSPKRRSR SPHRKWSDSSKQDDSPSGASYGQDYDLSPSRSHTSSNYDSYKKSPGSTSRRQSVSP PYKEPSAYQSSTRSPSPYSRRQRSVSPYSRRRSSSYERSGSYSGRSPSPYGRRRSSSP FLSKRSLSRSPLPSRKSMKSRSRSPAYSRHSSSHSKKKRSSSRSRHSSISPVRLPLNSS LGAELSRKKKERAAAAAAAKMDGKESKGSPVFLPRKENSSVEAKDSGLESKKLP RSVKLEKSAPDTELVNVTHLNTEVKNSSDTGKVKLDENSEKHLVKDLKAQGTRD

	SKPIALKEEIVTPKETETSEKETPPPLPTIASPPPPLPTTTPPPQTPPLPPLPPIPALPQQP PLPPSQPAFSQVPASSTSTLPPSTHSKTSAVSSQANSQPPVQVSVKTQVSVTAAIPHL KTSTLPPLPLPPLLPGDDDMDSPKETLPSKPVKKEKEQRTRHLLTDLPLPPELPGGD LSPPDSPEPKAITPPQQPYKKRPKICCPRYGERRQTESDWGKRCVDKFDIIGIIGEGT YGQVYKAKDKDTGELVALKKVRLDNEKEGFPITAIREIKILRQLIHRSVVNMKEIV TDKQDALDFKKDKGAFYLVFEYMDHDLMGLLESGLVHFSEDHIKSFMKQLMEGL EYCHKKNFLHRDIKCSNILLNNSGQIKLADFGLARLYNSEESRPYTNKVITLWYRP PELLLGEERYTPAIDVWSCGCILGELFTKKPIFQANLELAQLELISRLCGSPCPAVW PDVIKLPYFNTMKPKKQYRRRLREEFSFIPSAALDLLDHMLTLDPSKRCTAEQTLQ SDFLKDVELSKMAPPDLPHWQDCHELWSKKRRRQRQSGVVVEEPPPSKTSRKETT SGTSTEPVKNSSPAPPQPAPGKVESGAGDAIGLADITQQLNQSELAVLLNLLQSQT DLSIPQMAQLLNIHSNPEMQQQLEALNQSISALTEATSQQQDSETMAPEESLKEAP SAPVI**Q**PSAEQTTLEASSTPADMQNILAVLLSQLMKTQEPAGSLEENNSDKNSGPQ GPRRTPTMPQEEAAEKRPPEPPGPPPPPPPPPLVEGDLSSAPQELNPAVTAALLQLL SQPEAEPPGHLPHEHQALRPMEYSTRPRPNRTYGNTDGPETGFSAIDTDERNSGPA LTESLVQTLVKNRTFSGSLSHLGESSSYQGTGSVQFPGDQDLRFARVPLALHPVVG QPFLKAEGSSNSVVHAETKLQNYGELGPGTTGASSSGAGLHWGGPTQSSAYGKL YRGPTRVPPRGGRGRGVPY
10	MPNSERHGGKKDGSGGASGTLQPSSGGGSSNSRERHRLVSKHKRHKSKHSKDMG LVTPEAASLGTVIKPLVEYDDISSDSDTFSDDMAFKLDRRENDERRGSDRSDRLHK HRHHQHRRSRDLLKAKQTEKEKSQEVSSKSGSMKDRISGSSKRSNEETDDYGKAQ VAKSSSKESRSSKLHKEKTRKERELKSGHKDRSKSHRKRETPKSYKTVDSPKRRSR SPHRKWSDSSKQDDSPSGASYGQDYDLSPSRSHTSSNYDSYKKSPGSTSRRQSVSP PYKEPSAYQSSTRSPSPYSRRQRSVSPYSRRRSSSYERSGSYSGRSPSPYGRRRSSSP FLSKRSLSRSPLPSRKSMKSRSRSPAYSRHSSSHSKKKRSSSRSRHSSISPVRLPLNSS LGAELSRKKKERAAAAAAAKMDGKESKGSPVFLPRKENSSVEAKDSGLESKKLP RSVKLEKSAPDTELVNVTHLNTEVKNSSDTGKVKLDENSEKHLVKDLKAQGTRD SKPIALKEEIVTPKETETSEKETPPPLPTIASPPPPLPTTTPPPQTPPLPPLPPIPALPQQP PLPPSQPAFSQVPASSTSTLPPSTHSKTSAVSSQANSQPPVQVSVKTQVSVTAAIPHL KTSTLPPLPLPPLLPGDDDMDSPKETLPSKPVKKEKEQRTRHLLTDLPLPPELPGGD LSPPDSPEPKAITPPQQPYKKRPKICCPRYGERRQTESDWGKRCVDKFDIIGIIGEGT YGQVYKAKDKDTGELVALKKVRLDNEKEGFPITAIREIKILRQLIHRSVVNMKEIV TDKQDALDFKKDKGAFYLVFEYMDHDLMGLLESGLVHFSEDHIKSFMKQLMEGL

	EYCHKKNFLHRDIKCSNILLNNSGQIKLADFGLARLYNSEESRPYTNKVITLWYRP PELLLGEERYTPAIDVWSCGCILGELFTKKPIFQANLELAQLELISRLCGSPCPAVW PDVIKLPYFNTMKPKKQYRRRLREEFSFIPSAALDLLDHMLTLDPSKRCTAEQTLQ SDFLKDVELSKMAPPDLPHWQDCHELWSKKRRRQRQSGVVVEEPPPSKTSRKETT SGTSTEPVKNSSPAPPQPAPGKVESGAGDAIGLADITQQLNQSELAVLLNLLQSQT DLSIPQMAQLLNIHSNPEMQQQLEALNQSISALTEATSQQQDSETMAPEESLKEAP SAPVILPSAEQ**M**TLEASSTPADMQNILAVLLSQLMKTQEPAGSLEENNSDKNSGPQ GPRRTPTMPQEEAAEKRPPEPPGPPPPPPPPLVEGDLSSAPQELNPAVTAALLQLL SQPEAEPPGHLPHEHQALRPMEYSTRPRPNRTYGNTDGPETGFSAIDTDERNSGPA LTESLVQTLVKNRTFSGSLSHLGESSSYQGTGSVQFPGDQDLRFARVPLALHPVVG QPFLKAEGSSNSVVHAETKLQNYGELGPGTTGASSSGAGLHWGGPTQSSAYGKL YRGPTRVPPRGGRGRGVPY
11	MPNSERHGGKKDGSGGASGTLQPSSGGGSSNSRERHRLVSKHKRHKSKHSKDMG LVTPEAASLGTVIKPLVEYDDISSDSDTFSDDMAFKLDRRENDERRGSDRSDRLHK HRHHQHRRSRDLLKAKQTEKEKSQEVSSKSGSMKDRISGSSKRSNEETDDYGKAQ VAKSSSKESRSSKLHKEKTRKERELKSGHKDRSKSHRKRETPKSYKTVDSPKRRSR SPHRKWSDSSKQDDSPSGASYGQDYDLSPSRSHTSSNYDSYKKSPGSTSRRQSVSP PYKEPSAYQSSTRSPSPYSRRQRSVSPYSRRRSSSYERSGSYSGRSPSPYGRRRSSSP FLSKRSLSRSPLPRKSMKSRSRSPAYSRHSSSHSKKKRSSSRSRHSSISPVRLPLNSSL GAELSRKKKERAAAAAAAKMDGKESKGSPVFLPRKENSSVEAKDSGLESKKLPRS VKLEKSAPDTELVNVTHLNTEVKNSSDTGKVKLDENSEKHLVKDLKAQGTRDSK PIALKEEIVTPKETETSEKETPPPLPTIASPPPPLPTTTPPPQTPPLPPLPPIPALPQQPPL PPSQPAFSQVPASSTSTLPPSTHSKTSAVSSQANSQPPVQVSVKTQVSVTAAIPHLK TSTLPPLPLPPLLPGDDDMDSPKETLPSKPVKKEKEQRTRHLLTDLPLPPELPGGDL SPPDSPEPKAITPPQQPYKKRPKICCPRYGERRQTESDWGKRCVDKFDIIGIIGEGTY GQVYKAKDKDTGELVALKKVRLDNEKEGFPITAIREIKILRQLIHRSVVNMKEIVT DKQDALDFKKDKGAFYLVFEYMDHDLMGLLESGLVHFSEDHIKSFMKQLMEGLE YCHKKNFLHRDIKCSNILLNNSGQIKLADFGLARLYNSEESRPYTNKVITLWYRPP ELLLGEERYTPAIDVWSCGCILGELFTKKPIFQANLELAQLELISRLCGSPCPAVWP DVIKLPYFNTMKPKKQYRRRLREEFSFIPSAALDLLDHMLTLDPSKRCTAEQTLQS DFLKDVELSKMAPPDLPHWQDCHELWSKKRRRQRQSGVVVEEPPPSKTSRKETTS GTSTEPVKNSSPAPPQPAPGKVESGAGDAIGLADITQQLNQSELAVLLNLLQSQTD LS**V**PQMAQLLNIHSNPEMQQQLEALNQSISALTEATSQQQDSETMAPEESLKEAPS

	APVILPSAEQTTLEASST
12	MPNSERHGGKKDGSGGASGTLQPSSGGGSSNSRERHRLVSKHKRHKSKHSKDMG LVTPEAASLGTVIKPLVEYDDISSDSDTFSDDMAFKLDRRENDERRGSDRSDRLHK HRHHQHRRSRDLLKAKQTEKEKSQEVSSKSGSMKDRISGSSKRSNEETDDYGKAQ VAKSSSKESRSSKLHKEKTRKERELKSGHKDRSKSHRKRETPKSYKTVDSPKRRSR SPHRKWSDSSKQDDSPSGASYGQDYDLSPSRSHTSSNYDSYKKSPGSTSRRQSVSP PYKEPSAYQSSTRSPSPYSRRQRSVSPYSRRRSSSYERSGSYSGRSPSPYGRRRSSSP FLSKRSLSRSPLPRKSMKSRSRSPAYSRHSSSHSKKKRSSSRSRHSSISPVRLPLNSSL GAELSRKKKERAAAAAAAKMDGKESKGSPVFLPRKENSSVEAKDSGLESKKLPRS VKLEKSAPDTELVNVTHLNTEVKNSSDTGKVKLDENSEKHLVKDLKAQGTRDSK PIALKEEIVTPKETETSEKETPPPLPTIASPPPPLPTTTPPPQTPPLPPLPPIPALPQQPPL PPSQPAFSQVPASSTSTLPPSTHSKTSAVSSQANSQPPVQVSVKTQVSVTAAIPHLK TSTLPPLPLPPLLPGDDDMDSPKETLPSKPVKKEKEQRTRHLLTDLPLPPELPGGDL SPPDSPEPKAITPPQQPYKKRPKICCPRYGERRQTESDWGKRCVDKFDIIGIIGEGTY GQVYKAKDKDTGELVALKKVRLDNEKEGFPITAIREIKILRQLIHRSVVNMKEIVT DKQDALDFKKDKGAFYLVFEYMDHDLMGLLESGLVHFSEDHIKSFMKQLMEGLE YCHKKNFLHRDIKCSNILLNNSGQIKLADFGLARLYNSEESRPYTNKVITLWYRPP ELLLGEERYTPAIDVWSCGCILGELFTKKPIFQANLELAQLELISRLCGSPCPAVWP DVIKLPYFNTMKPKKQYRRRLREEFSFIPSAALDLLDHMLTLDPSKRCTAEQTLQS DFLKDVELSKMAPPDLPHWQDCHELWSKKRRRQRQSGVVVEEPPPSKTSRKETTS GTSTEPVKNSSPAPPQPAPGKVESGAGDAIGLADITQQLNQSELAVLLNLLQSQTD LSIPQMAQLLNIHSNPEMQQQLEALNQSISALTEATSQQQDSETMAPEESLKEAPS APVI**Q**PSAEQTTLEASST
13	MPNSERHGGKKDGSGGASGTLQPSSGGGSSNSRERHRLVSKHKRHKSKHSKDMG LVTPEAASLGTVIKPLVEYDDISSDSDTFSDDMAFKLDRRENDERRGSDRSDRLHK HRHHQHRRSRDLLKAKQTEKEKSQEVSSKSGSMKDRISGSSKRSNEETDDYGKAQ VAKSSSKESRSSKLHKEKTRKERELKSGHKDRSKSHRKRETPKSYKTVDSPKRRSR SPHRKWSDSSKQDDSPSGASYGQDYDLSPSRSHTSSNYDSYKKSPGSTSRRQSVSP PYKEPSAYQSSTRSPSPYSRRQRSVSPYSRRRSSSYERSGSYSGRSPSPYGRRRSSSP FLSKRSLSRSPLPRKSMKSRSRSPAYSRHSSSHSKKKRSSSRSRHSSISPVRLPLNSSL GAELSRKKKERAAAAAAAKMDGKESKGSPVFLPRKENSSVEAKDSGLESKKLPRS VKLEKSAPDTELVNVTHLNTEVKNSSDTGKVKLDENSEKHLVKDLKAQGTRDSK PIALKEEIVTPKETETSEKETPPPLPTIASPPPPLPTTTPPPQTPPLPPLPPIPALPQQPPL

	PPSQPAFSQVPASSTSTLPPSTHSKTSAVSSQANSQPPVQVSVKTQVSVTAAIPHLK TSTLPPLPLPPLLPGDDDMDSPKETLPSKPVKKEKEQRTRHLLTDLPLPPELPGGDL SPPDSPEPKAITPPQQPYKKRPKICCPRYGERRQTESDWGKRCVDKFDIIGIIGEGTY GQVYKAKDKDTGELVALKKVRLDNEKEGFPITAIREIKILRQLIHRSVVNMKEIVT DKQDALDFKKDKGAFYLVFEYMDHDLMGLLESGLVHFSEDHIKSFMKQLMEGLE YCHKKNFLHRDIKCSNILLNNSGQIKLADFGLARLYNSEESRPYTNKVITLWYRPP ELLLGEERYTPAIDVWSCGCILGELFTKKPIFQANLELAQLELISRLCGSPCPAVWP DVIKLPYFNTMKPKKQYRRRLREEFSFIPSAALDLLDHMLTLDPSKRCTAEQTLQS DFLKDVELSKMAPPDLPHWQDCHELWSKKRRRQRQSGVVVEEPPPSKTSRKETTS GTSTEPVKNSSPAPPQPAPGKVESGAGDAIGLADITQQLNQSELAVLLNLLQSQTD LSIPQMAQLLNIHSNPEMQQQLEALNQSISALTEATSQQQDSETMAPEESLKEAPS APVILPSAEQ**M**TLEASST
14	XADITQQLNQSELAVLLNLLQSQTDLS**V**PQMAQLLNIHSNPEMQQQLEALNQSISA LTEATSQQQDSETMAPEESLKEAPSAPVILPSAEQTTLEASSTPADMQNILAVLLSQ LMKTQEPAGSLEENNSDKNSGPQGPRRTPTMPQEEAAGRSNGGNAL
15	XADITQQLNQSELAVLLNLLQSQTDLSIPQMAQLLNIHSNPEMQQQLEALNQSISA LTEATSQQQDSETMAPEESLKEAPSAPVI**Q**PSAEQTTLEASSTPADMQNILAVLLSQ LMKTQEPAGSLEENNSDKNSGPQGPRRTPTMPQEEAAGRSNGGNAL
16	XADITQQLNQSELAVLLNLLQSQTDLSIPQMAQLLNIHSNPEMQQQLEALNQSISA LTEATSQQQDSETMAPEESLKEAPSAPVILPSAEQ**M**TLEASSTPADMQNILAVLLS QLMKTQEPAGSLEENNSDKNSGPQGPRRTPTMPQEEAAGRSNGGNAL

Pharmaceutical Compositions

[00229] In certain embodiments, the heteroaromatic CDK inhibitory compound described herein is administered as a pure chemical. In other embodiments, the heteroaromatic CDK inhibitory compound described herein is combined with a pharmaceutically suitable or acceptable carrier (also referred to herein as a pharmaceutically suitable (or acceptable) excipient, physiologically suitable (or acceptable) excipient, or physiologically suitable (or acceptable) carrier) selected on the basis of a chosen route of administration and standard pharmaceutical practice as described, for example, in *Remington: The Science and Practice of Pharmacy* (Gennaro, 21st Ed. Mack Pub. Co., Easton, PA (2005)).

[00230] Provided herein is a pharmaceutical composition comprising at least one heteroaromatic CDK inhibitory compound as described herein, or a stereoisomer, pharmaceutically acceptable salt, hydrate, or solvate thereof, together with one or more pharmaceutically acceptable carriers. The

carrier(s) (or excipient(s)) is acceptable or suitable if the carrier is compatible with the other ingredients of the composition and not deleterious to the recipient (*i.e.,* the subject or the patient) of the composition.

[00231] One embodiment provides a pharmaceutical composition comprising a pharmaceutically acceptable excipient and a compound of Formula (I), (II), (III), or (IV) or a compound disclosed in Tables 1-3, or a pharmaceutically acceptable salt or solvate thereof.

[00232] One embodiment provides a method of preparing a pharmaceutical composition comprising mixing a compound of Formula (I), (II), (III), or (IV), or a pharmaceutically acceptable salt or solvate thereof, and a pharmaceutically acceptable carrier.

[00233] In certain embodiments, the heteroaromatic CDK inhibitory compound as described by Formula (I), (II), (III), or (IV) or a compound disclosed in Tables 1-3, is substantially pure, in that it contains less than about 5%, or less than about 1%, or less than about 0.1%, of other organic small molecules, such as unreacted intermediates or synthesis by-products that are created, for example, in one or more of the steps of a synthesis method.

[00234] Suitable oral dosage forms include, for example, tablets, pills, sachets, or capsules of hard or soft gelatin, methylcellulose or of another suitable material easily dissolved in the digestive tract. In some embodiments, suitable nontoxic solid carriers are used which include, for example, pharmaceutical grades of mannitol, lactose, starch, magnesium stearate, sodium saccharin, talcum, cellulose, glucose, sucrose, magnesium carbonate, and the like. (*See*, *e.g.*, *Remington: The Science and Practice of Pharmacy* (Gennaro, 21st Ed. Mack Pub. Co., Easton, PA (2005)).

[00235] In some embodiments, the heteroaromatic CDK inhibitory compound as described by Formula (I), (II), (III), or (IV) or a compound disclosed in Tables 1-3, or pharmaceutically acceptable salt or solvate thereof, is formulated for administration by injection. In some instances, the injection formulation is an aqueous formulation. In some instances, the injection formulation is a non-aqueous formulation. In some instances, the injection formulation is an oil-based formulation, such as sesame oil, or the like.

[00236] The dose of the composition comprising at least one heteroaromatic CDK inhibitory compound as described herein differs depending upon the subject or patient's (e.g., human) condition. In some embodiments, such factors include general health status, age, and other factors.

[00237] Pharmaceutical compositions are administered in a manner appropriate to the disease to be treated (or prevented). An appropriate dose and a suitable duration and frequency of administration will be determined by such factors as the condition of the patient, the type and severity of the patient's disease, the particular form of the active ingredient, and the method of administration. In general, an appropriate dose and treatment regimen provides the composition(s) in an amount sufficient to

provide therapeutic and/or prophylactic benefit (e.g., an improved clinical outcome, such as more frequent complete or partial remissions, or longer disease-free and/or overall survival, or a lessening of symptom severity. Optimal doses are generally determined using experimental models and/or clinical trials. The optimal dose depends upon the body mass, weight, or blood volume of the patient.

[00238] Oral doses typically range from about 1.0 mg to about 1000 mg, one to four times, or more, per day.

Methods of Treatment

[00239] One embodiment provides a compound of Formula (I), (II), (III), or (IV) or a compound disclosed in Tables 1-3, or a pharmaceutically acceptable salt or solvate thereof, for use in a method of treatment of the human or animal body.

[00240] One embodiment provides a compound of Formula (I), (II), (III), or (IV) or a compound disclosed in Tables 1-3, or a pharmaceutically acceptable salt or solvate thereof, for use in a method of treatment of cancer, neoplastic disease, or hyperproliferative disorder.

[00241] One embodiment provides a use of a compound of Formula (I), (II), (III), or (IV) or a compound disclosed in Tables 1-3, or a pharmaceutically acceptable salt or solvate thereof, in the manufacture of a medicament for the treatment of cancer or neoplastic disease.

[00242] In some embodiments, described herein is a method of treating cancer in a patient in need thereof comprising administering to the patient a compound of Formula (I), or a pharmaceutically acceptable salt or solvate thereof. In some embodiments, described herein is a method of treating cancer in a patient in need thereof comprising administering to the patient a compound of Formula (II), or a pharmaceutically acceptable salt or solvate thereof. In some embodiments, described herein is a method of treating cancer in a patient in need thereof comprising administering to the patient a compound of Formula (III), or a pharmaceutically acceptable salt or solvate thereof. In some embodiments, described herein is a method of treating cancer in a patient in need thereof comprising administering to the patient a compound of Formula (IV), or a pharmaceutically acceptable salt or solvate thereof. In some embodiments, described herein is a method of treating cancer in a patient in need thereof comprising administering to the patient a compound disclosed in Table 1-3, or a pharmaceutically acceptable salt or solvate thereof. In some embodiments, also described herein is a method of treating cancer in a patient in need thereof comprising administering to the patient a pharmaceutical composition comprising a compound of Formula (I), or a pharmaceutically acceptable salt or solvate thereof, and a pharmaceutically acceptable excipient. In some embodiments, also described herein is a method of treating cancer in a patient in need thereof comprising administering to the patient a pharmaceutical composition comprising a

compound of Formula (II), or a pharmaceutically acceptable salt or solvate thereof, and a pharmaceutically acceptable excipient. In some embodiments, also described herein is a method of treating cancer in a patient in need thereof comprising administering to the patient a pharmaceutical composition comprising a compound of Formula (III), or a pharmaceutically acceptable salt or solvate thereof, and a pharmaceutically acceptable excipient. In some embodiments, also described herein is a method of treating cancer in a patient in need thereof comprising administering to the patient a pharmaceutical composition comprising a compound of Formula (IV), or a pharmaceutically acceptable salt or solvate thereof, and a pharmaceutically acceptable excipient. In some embodiments, also described herein is a method of treating cancer in a patient in need thereof comprising administering to the patient a pharmaceutical composition comprising a compound disclosed in Table 1-3, or a pharmaceutically acceptable salt or solvate thereof, and a pharmaceutically acceptable excipient. In some embodiments, the cancer is breast cancer, colorectal cancer, ovarian cancer, pancreatic cancer, prostate cancer, or lung cancer.

[00243] Provided herein is the method wherein the pharmaceutical composition is administered orally. Provided herein is the method wherein the pharmaceutical composition is administered by injection.

[00244] Other embodiments and uses will be apparent to one skilled in the art in light of the present disclosures. The following examples are provided merely as illustrative of various embodiments and shall not be construed to limit the invention in any way.

EXAMPLES

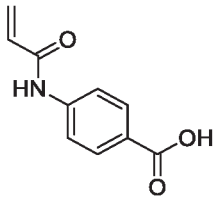
I. Chemical Synthesis

[00245] In some embodiments, the heteroaromatic CDK inhibitory compounds disclosed herein are synthesized according to the following examples. As used below, and throughout the description of the invention, the following abbreviations, unless otherwise indicated, shall be understood to have the following meanings:

^{o}C	degrees Celsius
δ_H	chemical shift in parts per million downfield from tetramethylsilane
DCM	dichloromethane (CH_2Cl_2)
DMF	dimethylformamide
DMSO	dimethylsulfoxide
EA	ethyl acetate
ESI	electrospray ionization
Et	ethyl

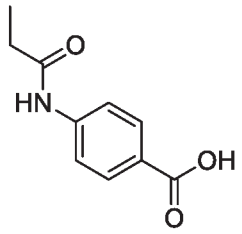
g	gram(s)
h	hour(s)
HPLC	high performance liquid chromatography
Hz	hertz
J	coupling constant (in NMR spectrometry)
LCMS	liquid chromatography mass spectrometry
μ	micro
m	multiplet (spectral); meter(s); milli
M	molar
M^+	parent molecular ion
Me	methyl
MHz	megahertz
min	minute(s)
mol	mole(s); molecular (as in mol wt)
mL	milliliter
MS	mass spectrometry
nm	nanometer(s)
NMR	nuclear magnetic resonance
pH	potential of hydrogen; a measure of the acidity or basicity of an aqueous solution
PE	petroleum ether
RT	room temperature
s	singlet (spectral)
t	triplet (spectral)
T	temperature
TFA	trifluoroacetic acid
THF	tetrahydrofuran

Example A1: Synthesis of Intermediate 1 (4-acrylamidobenzoic acid)



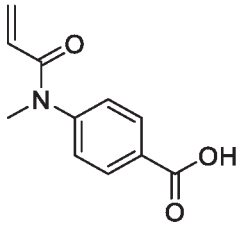
[00246] A mixture of 4-amino-benzoic acid (25 g, 181.9 mmol) and pyridine (10 mL) in DMF (200 mL) was cooled to 0 °C. Acryloyl chloride (22 mL, 272.8 mmol) was added and the solution was stirred at RT for 3 h. The reaction mixture was poured into water (200 mL) and the precipitate was filtered, washed with water, washed with PE, dried under high vacuum to give 4-acrylamidobenzoic acid as a white solid (22 g, 63%). MS Calcd.: 191, MS Found: 192 ($[M+H]^+$).

Example A2: Synthesis of Intermediate 2 (4-propionamidobenzoic acid)



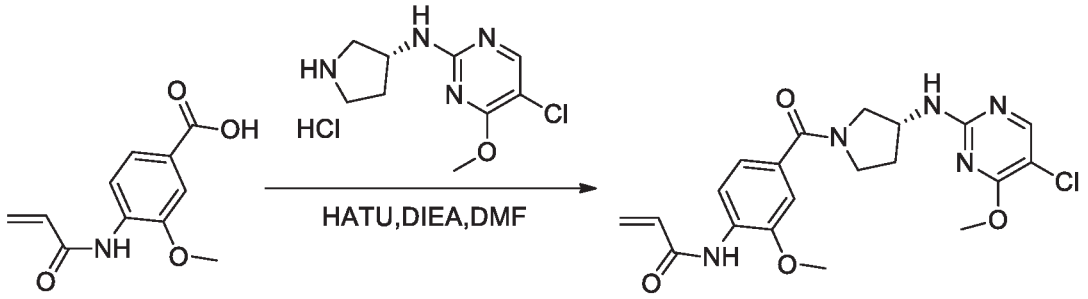
[00247] A mixture of 4-amino-benzoic acid (25 g, 181.9 mmol) and pyridine (10 mL) in DMF (200 mL) was cooled to 0 °C. Propionyl chloride (23.8 mL, 272.9 mmol) was added and the solution was stirred at RT for 16 h. The reaction mixture was poured into water (200 mL) and the precipitate was filtered, washed with water, washed with PE, dried under high vacuum to give 4-propionamidobenzoic acid as a white solid (22 g, 63%). MS Calcd.: 193, MS Found: 194 ($[M+H]^+$).

Example A3: Synthesis of 4-(N-methylacrylamido)benzoic acid



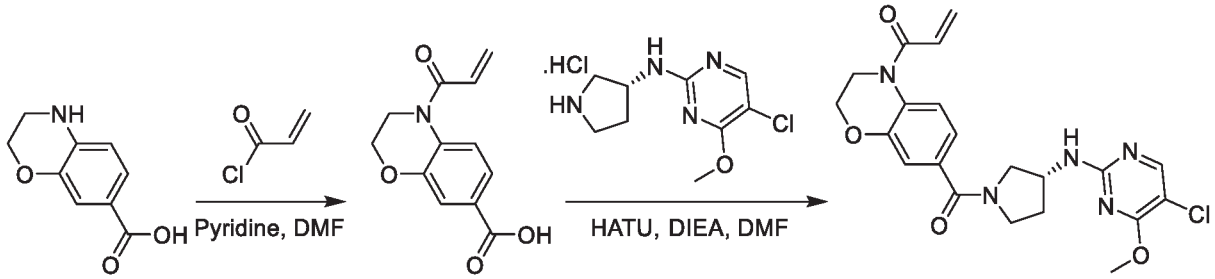
[00248] A solution of 4-(methylamino)benzoic acid (1.5 g, 10.0 mmol) in DMF (20 mL) and Pyridine (1.0 mL) was cooled to 0°C. To this cooled solution was added acryloyl chloride (1.4 g, 15.5 mmol). The reaction mixture was stirred at room temperature for 3h then poured into 20 mL of water. The resultant white solid was collected by filtration, washed with water and Petroleum Ether then dried under high vacuum to give 4-(N-methylacrylamido)benzoic acid (500 mg, 24%). MS Calcd.: 205, MS Found: 206 ([M+H]+).

Example 1: Synthesis of (R)-N-(4-(3-((5-chloro-4-methoxypyrimidin-2-yl)amino)pyrrolidine-1-carbonyl)-2-methoxyphenyl)acrylamide



[00249] A mixture of 4-acrylamido-3-methoxybenzoic acid (100 mg, 0.45 mmol), (R)-5-chloro-4-methoxy-N-(pyrrolidin-3-yl)pyrimidin-2-amine hydrochloride (112 mg, 0.49 mmol), HATU (256 mg, 0.67 mmol) and DIEA (145 mg, 1.12 mmol) in DMF (10 mL) was stirred at 25°C overnight. The mixture was diluted with H_2O (30 mL) and extracted with DCM (30 mL*2). The combined organic phases were concentrated *in vacuo*. The residue was purified by *prep*-HPLC to afford (R)-N-(4-(3-((5-chloro-4-methoxypyrimidin-2-yl)amino)pyrrolidine-1-carbonyl)-2-methoxyphenyl)acrylamide (13 mg, 7%). ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.89-2.11 (m, 1H), 2.12-2.29 (m, 1H), 3.42-3.55 (m, 4H), 3.64-3.94 (m, 6H), 4.30-4.52 (m, 1H), 5.73-5.75 (m, 1H), 6.23-6.27 (m, 1H), 6.75-6.79 (m, 1H), 7.12-7.19 (m, 2H), 7.73-7.75 (m, 1H), 8.09-8.16 (m, 2H), 9.51 (m, 1H). MS Calcd.: 431, MS Found: 432 ([M+H]$^+$).

Example 2: Synthesis of (R)-1-(7-(3-((5-chloro-4-methoxypyrimidin-2-yl)amino)pyrrolidine-1-carbonyl)-2H-benzo[b][1,4]oxazin-4(3H)-yl)prop-2-en-1-one



Step 1:

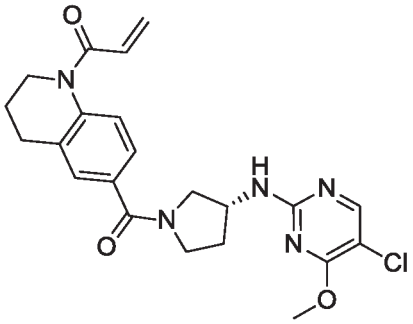
[00250] To a solution of 3,4-dihydro-2H-benzo[b][1,4]oxazine-7-carboxylic acid (500 mg, 2.82 mmol) in DMF (20 mL) was added pyridine (663 mg, 8.40 mmol) at 0°C. To the mixture was then added acryloyl chloride (510 mg, 5.64 mmol) dropwise over 5min. The mixture was then stirred at room temperature for overnight. The reaction mixture was concentrated *in vacuo* and the residue was purified by flash chromatography on silica gel (Petroleum Ether/Ethyl Acetate = 1/1) to afford 4-acryloyl-3,4-dihydro-2H-benzo[b][1,4]oxazine-7-carboxylic acid (150 mg, 23%). MS Calcd.: 233, MS Found: 234 ([M+H]$^+$).

Step 2:

[00251] The title compound was prepared in 32% yield from 4-acryloyl-3,4-dihydro-2H-benzo[b][1,4]oxazine-7-carboxylic acid using general procedure of N-{4-[3-(5-choro-4-methoxy-

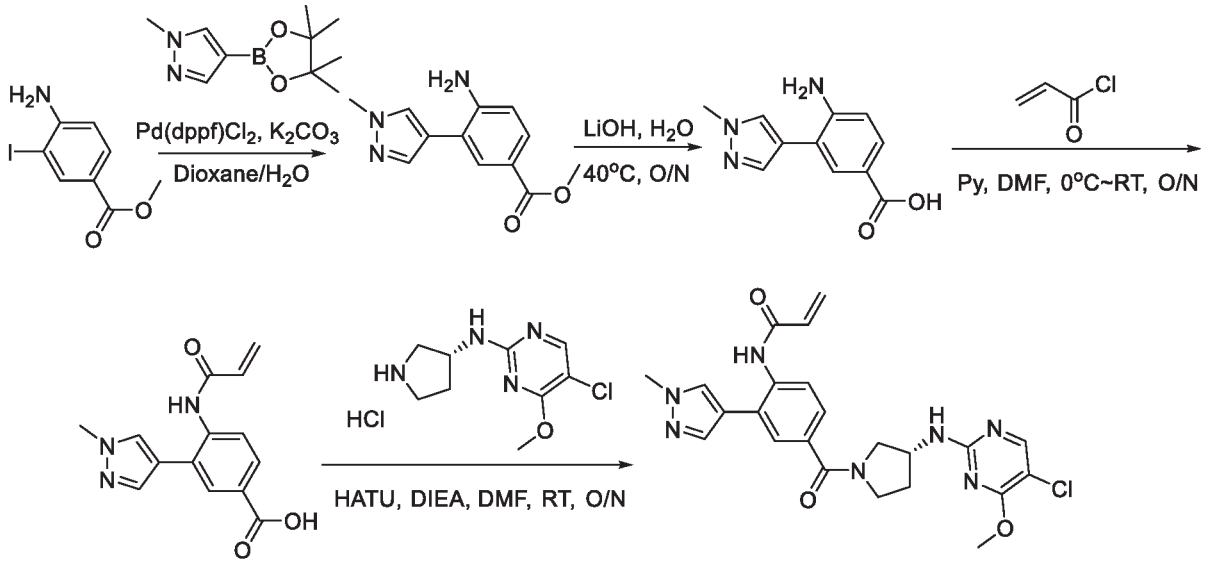
pyrimidin-2-ylamino)-piperidine-1-carbonyl]-2-methoxy-phenyl}-acrylamide. ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.91-2.13 (m, 2H), 3.50-3.95 (m, 9H), 4.30-4.31 (m, 3H), 5.83-5.85 (d, J = 8.0 Hz, 1H), 6.25-6.30 (d, J = 24.0 Hz, 1H), 6.78 (m, 1H), 7.02-7.08 (m, 2H), 7.49-7.67 (m, 2H), 8.08-8.14 (m, 1H). MS Calcd.: 443, MS Found: 444 ([M+H]$^+$)

Example 3: Synthesis of (R)-1-(6-(3-((5-chloro-4-methoxypyrimidin-2-yl)amino)pyrrolidine-1-carbonyl)-3,4-dihydroquinolin-1(2H)-yl)prop-2-en-1-one



[00252] The title compound was prepared in 18% yield from 1-acryloyl-1,2,3,4-tetrahydro-quinoline-6-carboxylic acid using general procedure of N-{4-[3-(5-choro-4-methoxy-pyrimidin-2-ylamino)-piperidine-1-carbonyl]-2-methoxy-phenyl}-acrylamide. ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.88-2.15 (m, 4H), 2.72-2.73 (m, 2H), 3.28-3.94 (m, 9H), 4.29-4.45 (m, 1H), 5.72 (d, J = 12.0 Hz, 1H), 6.22 (d, J = 8.8 Hz, 1H), 6.57 (d, J = 16.8 Hz, 1H), 7.35 (m, 3H), 7.67 (m, 1H), 8.11 (s, 1H). MS Calcd.: 441, MS Found: 442 ([M+H]$^+$).

Example 4: Synthesis of(R)-N-(4-(3-((5-chloro-4-methoxypyrimidin-2-yl)amino)pyrrolidine-1-carbonyl)-2-(1-methyl-1H-pyrazol-4-yl)phenyl)acrylamide



Step 1:

[00253] A suspension of methyl 4-amino-3-iodobenzoate (500 mg, 1.81 mmol), 1-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole (563 mg, 2.71 mmol), Pd(dppf)Cl_2 (132 mg, 0.18

mmol) and Cs_2CO_3 (1177 mg, 3.61 mmol) in Dioxane/H_2O (10 mL/2 mL) was stirred at 90°C for 8h under Nitrogen. The mixture was then diluted with H_2O (30 mL) and extracted with DCM (30 mL*2). The combined organic phases were concentrated *in vacuo* and the residue was purified by flash chromatography on silica gel (Petroleum Ether/Ethyl Acetate = 1/1) to afford methyl 4-amino-3-(1-methyl-1H-pyrazol-4-yl)benzoate (417 mg, 100%) as a brown solid. MS Calcd.: 231, MS Found: 232 ($[M+H]^+$).

Step 2:

[00254] A solution of 4-amino-3-(1-methyl-1H-pyrazol-4-yl)benzoate (417 mg, 1.81 mmol) and $LiOH \cdot H_2O$ (235 mg, 5.60 mmol) in THF/H_2O (20 mL/10 mL) was stirred at RT for 1 day. The reaction mixture was adjusted to pH=3 with HCl (2 M) and then extracted with DCM (30 mL). The organic layer was concentrated in vacuo to afford 4-amino-3-(1-methyl-1H-pyrazol-4-yl)benzoic acid (300 mg, 76%) as a brown solid. MS Calcd.: 217, MS Found: 218 ($[M+H]^+$).

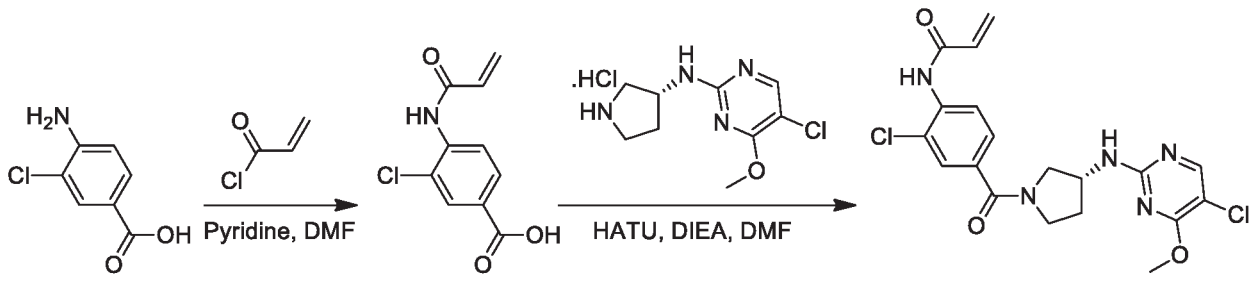
Step 3:

[00255] To a solution of 4-amino-3-(1-methyl-1H-pyrazol-4-yl)benzoic acid (300 mg, 1.38 mmol) in DMF (15 mL) was added pyridine (328 mg, 4.15 mmol) at 0°C. To the mixture was then added acryloyl chloride (250 mg, 2.76 mmol) dropwise over 5 min. The mixture was then stirred at RT overnight. Water (30 mL) was added and adjusted the pH to 3 with HCl (2 M), extracted with DCM (30 mL*2). The combined organic phases were concentrated *in vacuo* to afford 4-acrylamido-3-(1-methyl-1H-pyrazol-4-yl)benzoic acid (150 mg, 40%) as a brown solid. MS Calcd.: 271, MS Found: 272 ([M+H]+).

Step 4:

[00256] The title compound was prepared in 18% yield from 4-acrylamido-3-(1-methyl-1H-pyrazol-4-yl)benzoic acid using the general procedure of N-{4-[3-(5-choro-4-methoxy-pyrimidin-2-ylamino)-piperidine-1-carbonyl]-2-methoxy-phenyl}-acrylamide. ^1H NMR (400 MHz, DMSO-d_6): δ 1.95-2.17 (m, 2H), 3.39-3.70 (m, 3H), 3.82-3.95 (m, 7H), 4.27-4.45 (m, 1H), 5.75 (d, J = 10.4 Hz, 1H), 6.24 (d, J = 17.2 Hz, 1H), 6.49-6.53 (m, 1H), 7.35-7.41 (m, 1H), 7.55-7.69 (m, 4H), 7.98 (d, J = 10.0 Hz, 1H), 8.08-8.16 (m, 1H), 9.62 (s, 1H). MS Calcd.: 481, MS Found: 482 ([M+H]+).

Example 5: Synthesis of (R)-N-(2-chloro-4-(3-((5-chloro-4-methoxypyrimidin-2-yl)amino)pyrrolidine-1-carbonyl)phenyl)acrylamide



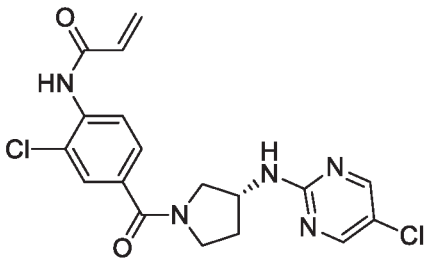
Step 1:

[00257] To a solution of 4-amino-3-chlorobenzoic acid (4.0 g, 23.3 mmol) in DMF (35 mL) was added pyridine (3.6 g, 45.6 mmol) at 0°C. To the mixture was then added acryloyl chloride (2.1 g, 23.2 mmol) dropwise over 3 min. The mixture was then stirred at RT overnight. The reaction was quenched with ice water (50 mL) and extracted with Ethyl Acetate (50 mL*2). The combined organic layers were collected, dried over Na_2SO_4, filtered, concentrated *in vacuo* and purified by column (Petroleum Ether/Ethyl Acetate = 1/1) to give 4-acrylamido-3-chlorobenzoic acid (700 mg, 11%). MS Calcd.: 225, MS Found: 226 ($[M+H]^+$).

Step 2:

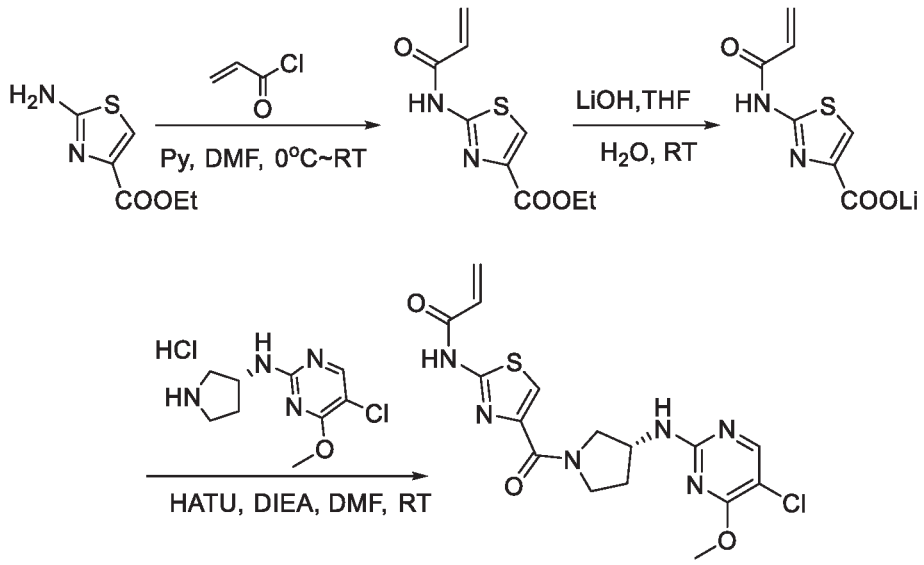
[00258] To a solution of 4-acrylamido-3-chlorobenzoic acid (150 mg, 0.67 mmol), (R)-5-chloro-4-methoxy-N-(pyrrolidin-3-yl)pyrimidin-2-amine hydrochloride (235 mg, 0.73 mmol) in DMF (15 mL) was added HATU (305 mg, 0.80 mmol) and DIEA (260 mg, 2.01 mmol) at 0°C. The mixture was stirred at RT overnight. The reaction was concentrated *in-vacuo* and purified by *prep*-HPLC to give (R)-N-(2-chloro-4-(3-((5-chloro-4-methoxypyrimidin-2-yl)amino)pyrrolidine-1-carbonyl)phenyl)acrylamide (130 mg, 44%). ^1H NMR (400 MHz, DMSO-d_6): δ 1.90-2.14 (m, 2H), 3.39-3.94 (m, 7H), 4.27-4.44 (m, 1H), 5.79-5.82 (m, 1H), 6.27-6.32 (m, 1H), 6.62-6.69 (m, 1H), 7.50 (m, 1H), 7.62-7.67 (m, 2H), 7.89-7.91 (m, 1H), 8.08-8.14 (m, 1H), 9.79-9.80 (m, 1H). MS Calcd.: 435, MS Found: 436 ($[M+H]^+$).

Example 6: Synthesis of (R)-N-(2-chloro-4-(3-((5-chloropyrimidin-2-yl)amino)pyrrolidine-1-carbonyl)phenyl)acrylamide



[00259] The title compound was prepared in 6% yield from 4-acrylamido-3-chlorobenzoic acid using general procedure of (R)-N-(2-chloro-4-(3-((5-chloro-4-methoxypyrimidin-2-yl)amino)pyrrolidine-1-carbonyl)phenyl)acrylamide. ^1H NMR (400 MHz, DMSO-d_6): δ 1.98-2.14 (m, 2H), 3.38-3.74 (m, 4H), 4.27-4.42 (m, 1H), 5.90-5.82 (m, 1H), 6.27-6.32 (d, J = 20 Hz, 1H), 6.64-6.69 (m, 1H), 7.48-7.49 (m, 1H), 7.62-7.66 (m, 1H), 7.82 (m, 1H), 7.91 (m, 1H), 8.32-8.38 (m, 1H), 9.78-9.80 (m, 1H). MS Calcd.: 405, MS Found: 406 ($[M+H]^+$).

Example 7: Synthesis of (R)-N-(4-(3-((5-chloro-4-methoxypyrimidin-2-yl)amino)pyrrolidine-1-carbonyl)thiazol-2-yl)acrylamide



Step 1:

[00260] To a solution of ethyl 2-aminothiazole-4-carboxylate (5.0 g, 29.0 mmol) in DMF (35 mL) was added pyridine (2.5 mL) at 0°C. Then to the mixture was added acryloyl chloride (3.5 mL, 43.6 mmol) dropwise over 3min and the mixture was then stirred at RT overnight. The reaction mixture was quenched with water (50 mL) and extracted with Ethyl Acetate (50 mL*3). The combined organic layers were washed with water (100 mL*2) and brine (100 mL). The organic layer was collected, dried over Na_2SO_4, filtered, concentrated *in vacuo* and purified by flash chromatography on silica gel (Petroleum Ether/Ethyl Acetate = 1/1) to give ethyl 2-acrylamidothiazole-4-carboxylate (1.5 g, 23%). MS Calcd.: 226, MS Found: 227 ($[M+H]^+$).

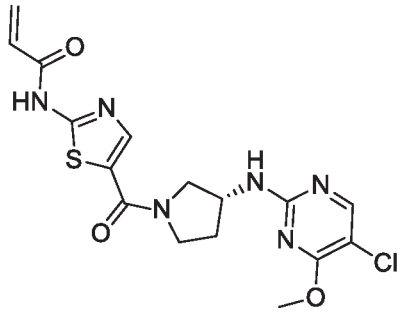
Step 2:

[00261] To a solution of 2-acrylamidothiazole-4-carboxylate (500 mg, 2.22 mmol) in THF (15 mL) and water (15mL) was added $LiOH.H_2O$ (93 mg, 2.22 mmol). The mixture was then stirred at RT overnight. The reaction progress was monitored by LCMS (50% starting material and 50% product was formed). To the reaction was then added $LiOH.H_2O$ (46 mg, 1.10 mmol) and the mixture was stirred at RT overnight. The reaction mixture was concentrated *in-vacuo* to afford lithium 2-acrylamidothiazole-4-carboxylate (400 mg, 23%). MS Calcd.: 198, MS Found: 199 ($[M+H]^+$).

Step 3:

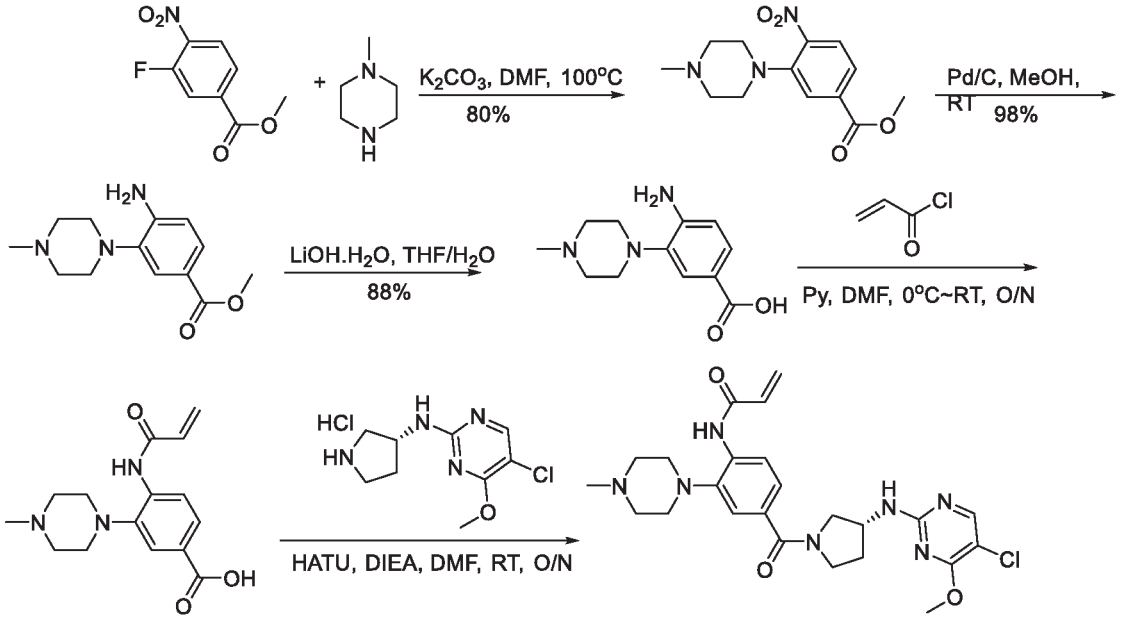
[00262] The title compound was prepared in 14% yield from lithium salt of 2-acryloylamino-thiazole-4-carboxylic acid using general procedure of N-{4-[3-(5-Chloro-4-methoxy-pyrimidin-2-ylamino)-pyrrolidine-1-carbonyl]-thiazol-2-yl}-acrylamide. ^1H NMR (400 MHz, DMSO-d_6): δ 1.99-2.0 (m, 1H), 2.1-2.15 (m, 1H), 3.67-3.69 (m, 3H), 3.97-4.0 (m, 3H), 4.1-4.4 (m, 2H), 5.89-5.92 (m, 1H), 6.40 (d, J = 12.0 Hz, 1H), 6.51-6.52 (m, 1H), 7.67 (s, 1H), 7.7 (s, 1H), 8.12 (d, J = 16.0 Hz, 1H), 12.39 (s, 1H). MS Calcd.: 408, MS Found: 409 ($[M+H]^+$).

Example 8: Synthesis of (R)-N-(5-(3-((5-chloro-4-methoxypyrimidin-2-yl)amino)pyrrolidine-1-carbonyl)thiazol-2-yl)acrylamide



[00263] The title compound was prepared in 2% yield from 2-acrylamidothiazole-5-carboxylic acid using general procedure of N-{4-[3-(4-Cyclopentyloxy-pyrimidin-2-ylamino)-piperidine-1-carbonyl]-phenyl}-acrylamide. ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.98-1.99 (m, 1H), 2.07-2.25 (m, 1H), 3.52-3.69 (m, 3H), 3.85-3.92 (m, 3H), 4.08 (s, 1H), 4.38-4.43 (m, 1H), 5.93-5.95 (m, 1H), 6.40-6.44 (m, 1H), 6.50-6.53 (m, 1H), 7.75 (s, 1H), 7.94-7.99 (m, 1H), 8.14 (s, 1H), 12.58 (s, 1H). MS Calcd.: 408, MS Found: 409 ([M+H]$^+$).

Example 9: Synthesis of (R)-N-(4-(3-((5-chloro-4-methoxypyrimidin-2-yl)amino)pyrrolidine-1-carbonyl)-2-(4-methylpiperazin-1-yl)phenyl)acrylamide



Step 1:

[00264] A suspension of methyl 3-fluoro-4-nitrobenzoate (1.1 g, 5.4 mmol), 1-methyl-piperazine (0.6 g, 5.9 mmol) and K_2CO_3 (1.5 g, 1.1 mmol) in DMF (30 mL) was stirred at 100°C overnight. The reaction mixture was diluted with water (100 mL) and extracted with Ethyl Acetate (50 mL*3). The combined organic layers were washed with water (100 mL*2) and brine (100 mL), dried over

Na_2SO_4, filtered and concentrated *in vacuo* to give methyl 3-(4-methylpiperazin-1-yl)-4-nitrobenzoate (1.2 g, 80%). MS Calcd.: 279, MS Found: 280 ($[M+H]^+$).

Step 2:

[00265] A suspension of methyl 3-(4-methylpiperazin-1-yl)-4-nitrobenzoate (1.5 g, 5.7 mmol) and Pd/C (400 mg, 5%) in MeOH (30 mL) was stirred at room temperature for overnight under 1atm H_2. The reaction was filtered and concentrated *in vacuo* to give methyl 4-amino-3-(4-methylpiperazin-1-yl)benzoate (1.3 g, 98%). MS Calcd.: 249, MS Found: 250 ($[M+H]^+$).

Step 3:

[00266] A suspension of methyl 4-amino-3-(4-methylpiperazin-1-yl)benzoate (1.8 g, 6.5 mmol) and $LiOH.H_2O$ (540 mg, 12.9 mmol) in THF (30 mL) and water (10 mL) was stirred at RT overnight. The reaction was concentrated to remove THF, acidified to pH 5, filtered and then dried *in vacuo* to afford 4-amino-3-(4-methylpiperazin-1-yl)benzoic acid (1.5 g, 88%). MS Calcd.: 235, MS Found: 236 ($[M+H]^+$).

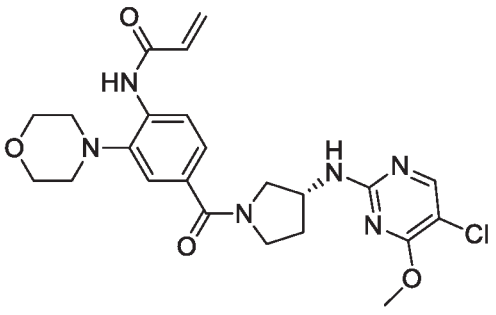
Step 4:

[00267] The title compound was prepared in 40% yield from 4-amino-3-(4-methylpiperazin-1-yl)benzoic acid using general procedure of 4-acrylamido-3-chlorobenzoic acid. MS Calcd.: 289, MS Found: 290 ($[M+H]^+$).

Step 5:

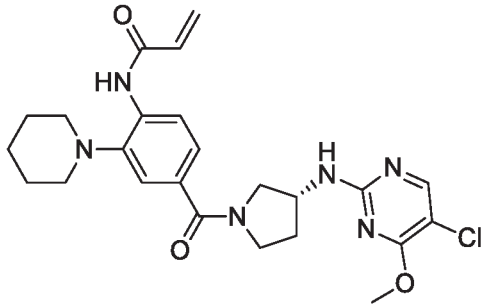
[00268] The title compound was prepared in 6% yield from 4-acrylamido-3-(4-methylpiperazin-1-yl)benzoic acid using general procedure of (R)-N-(4-(3-((5-chloro-4-methoxypyrimidin-2-yl)amino)pyrrolidine-1-carbonyl)-2-(4-methylpiperazin-1-yl)phenyl)acrylamide. ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.90-2.12 (m, 1H), 2.12-2.20 (m, 1H), 2.25 (s, 3H), 2.51-2.54 (m, 4H), 2.79-2.84 (m, 4H), 3.40-3.43 (m, 1H), 3.50-3.54 (m, 1H), 3.62-3.66 (m, 1H), 3.75-3.76 (m, 1H), 3.86 (s, 1.55H), 3.94 (s, 1.45H), 4.25-4.42 (m, 1H), 5.78 (d, J = 10.4 Hz, 1H), 6.26 (d, J = 16.8 Hz, 1H), 6.60-6.67 (m, 1H), 7.22-7.32 (m, 2H), 7.68 (br s, 1H), 8.00-8.14 (s, 2H), 9.08 (s, 0.55H), 9.10 (s, 0.45H). MS Calcd.: 499, MS Found: 500 ([M+H]+).

Example 10: Synthesis of (R)-N-(4-(3-((5-chloro-4-methoxypyrimidin-2-yl)amino)pyrrolidine-1-carbonyl)-2-morpholinophenyl)acrylamide



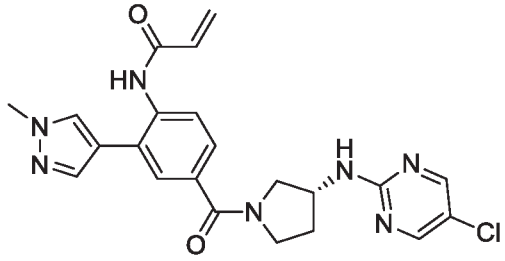
[00269] The title compound was prepared in 38% yield from 4-acrylamido-3-morpholinobenzoic acid using general procedure of N-{4-[3-(4-cyclopentyloxy-pyrimidin-2-ylamino)-piperidine-1-carbonyl]-phenyl}-acrylamide. ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.90-2.12 (m, 1H), 2.12-2.20 (m, 1H), 2.79-2.83 (m, 4H), 3.40-3.50 (m, 1H), 3.50-3.54 (m, 1H), 3.62-3.66 (m, 1H), 3.79-3.95 (m, 8H), 4.26-4.30 (m, 1H), 5.79 (d, J = 10.0 Hz, 1H), 6.27 (d, J = 16.4 Hz, 1H), 6.60-6.67 (m, 1H), 7.27-7.34 (m, 2H), 7.69 (br s, 1H), 8.07-8.16 (s, 2H), 9.20 (s, 0.55H), 9.22 (s, 0.45H). MS Calcd.: 486, MS Found: 487 ([M+H]$^+$).

Example 11: Synthesis of (R)-N-(4-(3-((5-chloro-4-methoxypyrimidin-2-yl)amino)pyrrolidine-1-carbonyl)-2-(piperidin-1-yl)phenyl)acrylamide



[00270] The title compound was prepared in 6% yield from 4-acrylamido-3-(piperidin-1-yl)benzoic acid using general procedure of N-{4-[3-(4-cyclopentyloxy-pyrimidin-2-ylamino)-piperidine-1-carbonyl]-phenyl}-acrylamide. ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.53 (s, 2H), 1.70 (s, 4H), 1.98-2.01 (m, 1H), 2.14-2.16 (m, 1H), 2.71-2.77 (m, 4H), 3.40-3.44 (m, 2H), 3.65-3.94 (m, 5H), 4.24-4.50 (m, 1H), 5.79 (d, J = 10.0 Hz, 1H), 6.26 (d, J = 16.4 Hz, 1H), 6.63-6.70 (m, 1H), 7.21-7.31 (m, 2H), 7.71 (br s, 1H), 8.02-8.15 (s, 2H), 9.09 (s, 0.55H), 9.11 (s, 0.45H). MS Calcd.: 484, MS Found: 485 ([M+H]$^+$).

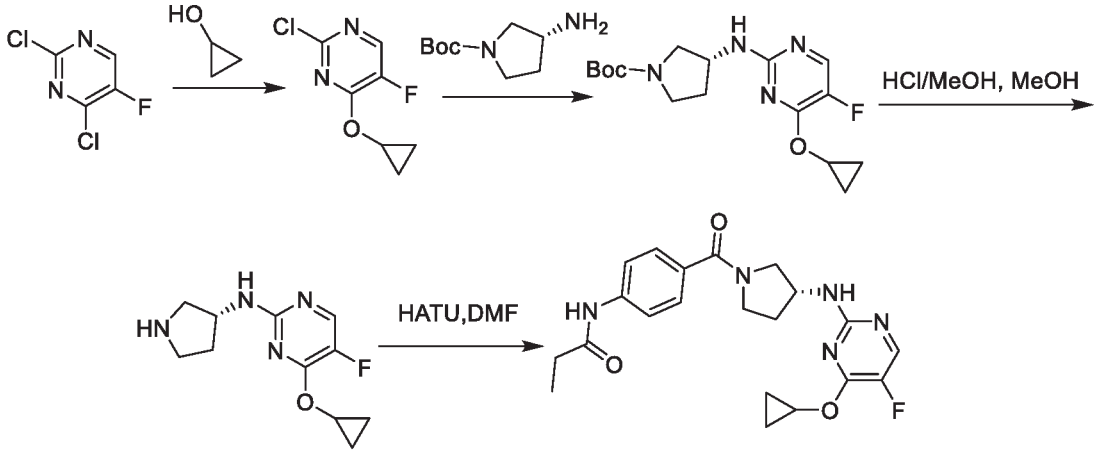
Example 12: Synthesis of (R)-N-(4-(3-((5-chloropyrimidin-2-yl)amino)pyrrolidine-1-carbonyl)-2-(1-methyl-1H-pyrazol-4-yl)phenyl)acrylamide



[00271] The title compound was prepared in 39% yield from 4-acrylamido-3-(1-methyl-1H-pyrazol-4-yl)benzoic acid using general procedure of N-{4-[3-(4-Cyclopentyloxy-pyrimidin-2-ylamino)-piperidine-1-carbonyl]-phenyl}-acrylamide. ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.90-2.12 (m, 1H), 2.12-2.20 (m, 1H), 3.37-3.45 (m, 1H), 3.54-3.67 (m, 1H), 3.74-3.80 (m, 2H), 3.86 (s, 3H), 4.23-4.42 (m, 1H), 5.75 (d, J = 10.0 Hz, 1H), 6.24 (d, J = 16.4 Hz, 1H), 6.51-6.67 (m, 1H), 7.35-7.40

(m, 1H), 7.55-7.68 (m, 3H), 7.81 (br s, 1H), 7.98 (d, J = 8.4 Hz, 1H), 8.31-8.38 (m, 2H), 9.20 (s, 0.55H), 9.22 (s, 0.45H). MS Calcd.: 451, MS Found: 452 ($[M+H]^+$).

Example 13: Synthesis of (R)-N-(4-(3-((4-cyclopropoxy-5-fluoropyrimidin-2-yl)amino)pyrrolidine-1-carbonyl)phenyl)propionamide



Step 1:

[00272] To a solution of cyclopropanol (3.3 g, 20.0 mmol) in THF (60 mL) was added NaH (880 mg, 22.0 mmol, 60% in oil) at 0°C. The reaction mixture was then stirred at 0°C for 20 min. A solution of 2,4-dichloro-5-fluoropyrimidine in THF (10 mL) was then added and the mixture was stirred at 0°C for 4 hours. Sat. NH_4Cl (20 mL) was added to quench the reaction and the mixture was extracted with Ethyl Acetate (500 mL). The organic layer was washed with water (500 mL*3) and concentrated *in vacuo* to afford 2-chloro-4-cyclopropoxy-5-fluoropyrimidine (3.76 g, 100%) as yellow oil. ^1H NMR (400 MHz, $CDCl_3$): δ 0.89 (s, 4H), 4.49-4.54 (m, 1H), 8.15 (d, J = 2.0 Hz, 1H).

Step 2:

[00273] A solution of 2-chloro-4-cyclopropoxy-5-fluoropyrimidine (1.9 g, 10 mmol), (R)-tert-butyl 3-aminopyrrolidine-1-carboxylate (1.9 g, 10.0 mmol) and DIEA (3.9 g, 30.0 mmol) in NMP (30 mL) was stirred at 130°C for 8 hours. The mixture was cooled to room temperature and diluted with Ethyl Acetate (500 mL). The organic layer was then washed with water (500 mL*2) and brine (100 mL), dried over Na_2SO_4, then filtered and concentrated *in vacuo*. The residue was purified by reverse-chromatography column ACN/H_2O (5-95%, RT=30min), to afford (R)-tert-butyl 3-((4-cyclopropoxy-5-fluoropyrimidin-2-yl)amino)pyrrolidine-1-carboxylate (1.8 g, 53%) as black oil. ^1H NMR (400 MHz, $CDCl_3$): δ 0.79-0.86 (m, 4H), 1.46 (s, 9H), 1.90 (br s, 1H), 2.19-2.24 (m,

1H), 3.20-3.49 (m, 3H), 3.70-3.74 (m, 1H), 4.32-4.41 (m, 2H), 5.03-5.05 (m, 1H), 7.91 (d, J = 2.8 Hz, 1H).

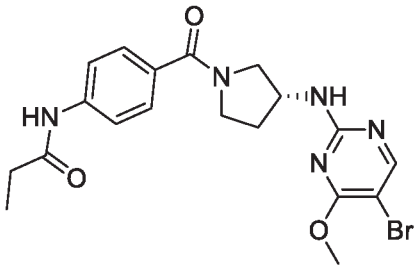
Step 3:

[00274] To a solution of (R)-tert-butyl 3-((4-cyclopropoxy-5-fluoropyrimidin-2-yl)amino)pyrrolidine-1-carboxylate (1.5 g, 4.48 mmol) in MeOH (2 mL) was added HCl/MeOH (8 mL, 1M). The mixture was stirred at room temperature for 8 hours. The mixture was concentrated to afford (R)-4-cyclopropoxy-5-fluoro-N-(pyrrolidin-3-yl)pyrimidin-2-amine (1.0 g, 100%). MS Calcd.: 238, MS Found: 239 ($[M+H]^+$).

Step 4:

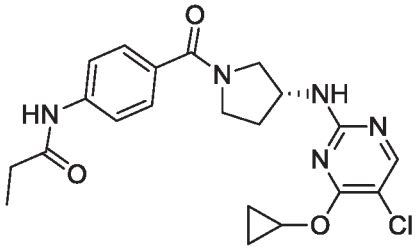
[00275] The title compound was prepared in 21.4% yield from (R)-4-cyclopropoxy-5-fluoro-N-(pyrrolidin-3-yl)pyrimidin-2-amine according to the procedure for the preparation of N-{4-[3-(4-Cyclopropoxy-5-fluoro-pyrimidin-2-ylamino)-pyrrolidine-1-carbonyl]-phenyl}-propionamide. ^{1}H NMR (400 MHz, DMSO-d_6): δ 0.56-0.79 (m, 4H), 1.06-1.10 (m, 3H), 1.86-2.17 (m, 2H), 2.31-2.37 (m, 2H), 3.39-3.84 (m, 4H), 4.18-4.37 (m, 2H), 7.46-7.51 (m, 3H), 7.61-7.66 (m, 2H), 8.06-8.15 (m, 1H), 10.05 (s, 1H). MS Calcd.: 413; Found: 414 ($[M+H]^+$).

Example 14: Synthesis of (R)-N-(4-(3-((5-bromo-4-methoxypyrimidin-2-yl)amino)pyrrolidine-1-carbonyl)phenyl)propionamide



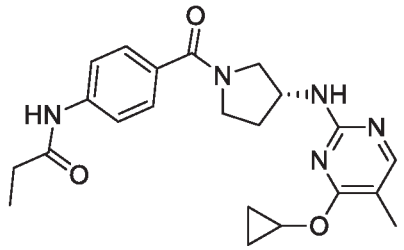
[00276] The title compound was prepared in 17.9% yield from (R)-5-bromo-4-methoxy-N-(pyrrolidin-3-yl)pyrimidin-2-amine according to the procedure for the preparation of (R)-N-(4-(3-((4-cyclopropoxy-5-fluoropyrimidin-2-yl)amino)pyrrolidine-1-carbonyl)phenyl)propionamide. ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.06-1.10 (m, 3H), 1.90-2.14 (m, 2H), 2.31-2.36 (m, 2H), 3.37-3.64 (m, 3H), 3.74-3.93 (m, 4H), 4.25-4.42 (m, 1H), 7.46-7.51 (m, 2H), 7.61-7.74 (m, 3H), 8.14-8.21 (m, 1H), 10.04 (s, 1H). MS Calcd.: 447; Found: 448 ($[M+H]^+$)..

Example 15: Synthesis of (R)-N-(4-(3-((5-chloro-4-cyclopropoxypyrimidin-2-yl)amino)pyrrolidine-1-carbonyl)phenyl)propionamide



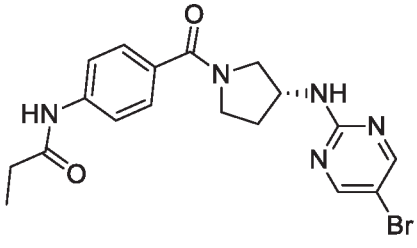
[00277] The title compound was prepared in 29 % yield from (5-Chloro-4-cyclopropoxy-pyrimidin-2-yl)-pyrrolidin-3-yl-amine according to the procedure for the preparation of (R)-N-(4-(3-((4-cyclopropoxy-5-fluoropyrimidin-2-yl)amino)pyrrolidine-1-carbonyl)phenyl)propionamide; ^{1}H NMR (400 MHz, DMSO-d_6): δ 0.68-0.80 (m, 4H), 1.08 (t, J = 7.2 Hz, 3H), 1.91-2.07 (m, 1H), 2.13-2.18 (m, 1H), 2.31-2.36 (m, 2H), 3.34-3.47 (m, 1H), 3.49-3.55 (m, 1H), 3.59-3.67 (m, 1H), 3.74-3.88 (m, 1H), 4.15-4.27 (m, 1H), 4.32-4.37 (m, 1H), 7.45-7.50 (m, 2H), 7.61-7.71 (m, 3H), 8.07-8.15 (m, 1H), 10.02 (s, 1H). MS Calcd.: 429; Found: 430 ([M+H]$^+$).

Example 16: Synthesis of (R)-N-(4-(3-((4-cyclopropoxy-5-methylpyrimidin-2-yl)amino)pyrrolidine-1-carbonyl)phenyl)propionamide



[00278] The title compound was prepared in 20.9% yield from (R)-4-cyclopropoxy-5-methyl-N-(pyrrolidin-3-yl)pyrimidin-2-amine according to the procedure for the preparation of (R)-N-(4-(3-((4-cyclopropoxy-5-fluoropyrimidin-2-yl)amino)pyrrolidine-1-carbonyl)phenyl)propionamide ^{1}H NMR (400 MHz, DMSO-d_6): δ 0.54-0.85 (m, 4H), 1.06-1.10 (m, 3H), 1.81-1.86 (m, 3H), 1.91-2.16 (m, 2H), 2.30-2.36 (m, 2H), 3.35-3.87 (m,4H), 4.19-4.41 (m, 2H), 7.16 (s, 1H), 7.44-7.48 (m, 2H), 7.50-7.65 (m, 2H), 7.80-7.88 (m, 1H), 10.01 (s, 1H). [M+H] Calcd.: 409; Found: 410 ([M+H]$^+$).

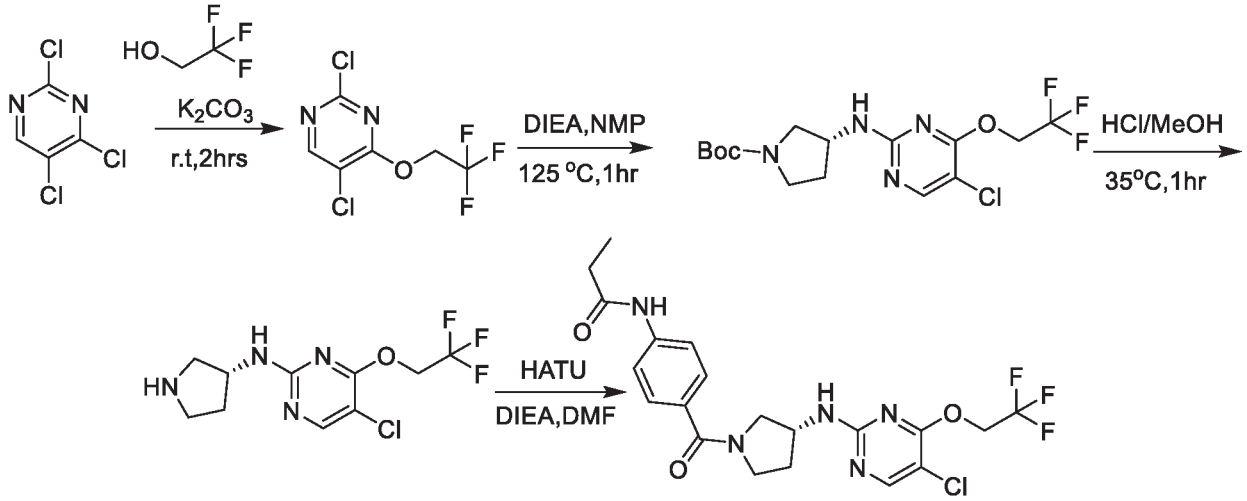
Example 17: Synthesis of (R)-N-(4-(3-((5-bromopyrimidin-2-yl)amino)pyrrolidine-1-carbonyl)phenyl)propionamide



[00279] The title compound was prepared in 16.5% yield from (R)-5-bromo-N-(pyrrolidin-3-yl)pyrimidin-2-amine according to the procedure for the preparation of (R)-N-(4-(3-((5-bromopyrimidin-2-

yl)amino)pyrrolidine-1-carbonyl)phenyl)propionamide. ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.06-1.13 (m, 3H), 1.86-2.26 (m, 2H), 2.32-2.38 (m, 2H), 3.40-3.77 (m, 4H), 4.16-4.40 (m, 1H), 7.45-7.50 (m, 2H), 7.61-7.65 (m, 2H), 7.78-7.80 (m, 1H) ,8.34-8.42 (m, 2H), 9.98-10.01 (m, 1H). Calcd.: 417; Found: 418 ([M+H]$^+$).

Example 18: Synthesis of (R)-N-(4-(3-((5-chloro-4-(2,2,2-trifluoroethoxy)pyrimidin-2-yl)amino)pyrrolidine-1-carbonyl)phenyl)propionamide



Step 1:

[00280] A mixture of 2,4,5-trichloropyrimidine (1.0 g, 5.46 mmol) and K_2CO_3 (753 mg, 5.46 mmol) in 2,2,2-trifluoroethanol (5 mL) was stirred at room temperature for 2hrs. The mixture was diluted with Ethyl Acetate (100 mL) and filtered. The filtrate was concentrated in-vacuo to afford 2,5-dichloro-4-(2,2,2-trifluoroethoxy)pyrimidine (1.35 g, 100%) as colorless oil. ^{1}H NMR (400 MHz, CD_3Cl): δ 4.84-4.90 (m, 2H), 8.44 (s, 1H).

Step 2:

[00281] A solution of 2,5-dichloro-4-(2,2,2-trifluoroethoxy)pyrimidine (1.4 g, 5.4 mmol), (R)-tert-butyl 3-aminopyrrolidine-1-carboxylate (1.0 g, 5.4 mmol) and DIEA (1.4 g, 10.8 mmol) in NMP (6 mL) was stirred at 125°C for 1 hour. The mixture was cooled to rt and diluted with Ethyl Acetate (500 mL). The organic layer was washed with water (500 mL*2) and brine (100 mL), dried over Na_2SO_4, filtered and concentrated in vacuo. The residue was purified by reverse-chromatography column ACN/H_2O (5-95%, RT=30min), to afford (R)-tert-butyl 3-((5-chloro-4-(2,2,2-trifluoroethoxy)pyrimidin-2-yl)amino)pyrrolidine-1-carboxylate (1.4 g, 64%) as colorless oil. MS Calcd.: 396, MS Found: 397 ([M+H]$^+$).

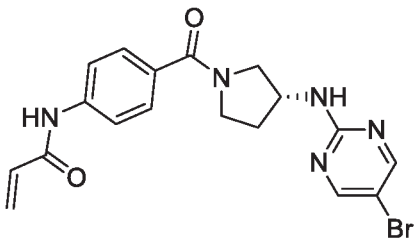
Step 3:

[00282] To a solution of (R)-tert-butyl 3-((5-chloro-4-(2,2,2-trifluoroethoxy)pyrimidin-2-yl)amino)pyrrolidine-1-carboxylate (1.4 g, 3.5 mmol) in MeOH (2 mL) was added HCl/MeOH (8 mL, 1M). The mixture was stirred at 35°C for 2 hours. The mixture was concentrated to afford (R)-5-chloro-N-(pyrrolidin-3-yl)-4-(2,2,2-trifluoroethoxy)pyrimidin-2-amine (730 mg, 69%). MS Calcd.: 296, MS Found: 297 ($[M+H]^+$).

Step 4:

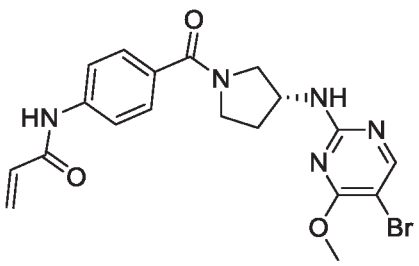
[00283] The title compound was prepared in 46% yield from (R)-5-chloro-N-(pyrrolidin-3-yl)-4-(2,2,2-trifluoroethoxy)pyrimidin-2-amine according to the procedure for the preparation of (R)-N-(4-(3-((4-cyclopropoxy-5-fluoropyrimidin-2-yl)amino)pyrrolidine-1-carbonyl)phenyl)propionamide. ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.08 (t, J = 7.2 Hz, 3H), 1.88-1.99 (m, 1H), 2.11-2.16 (m, 1H), 2.31-2.34 (m, 2H), 3.41-3.44 (m, 1H), 3.51-3.53(m, 1H), 3.62-3.64 (m, 1H), 3.77-3.78 (m, 1H), 4.28-4.24 (m, 1H), 4.99-5.11 (m, 2H), 7.46-7.51 (m, 2H), 7.61-7.66 (m, 2H), 7.84-7.93 (m, 1H), 8.20-8.27 (m, 1H), 10.03(s, 1H). MS Calcd.: 471; Found, 472 ($[M+H]^+$).

Example 19: Synthesis of (R)-N-(4-(3-((5-bromopyrimidin-2-yl)amino)pyrrolidine-1-carbonyl)phenyl)acrylamide



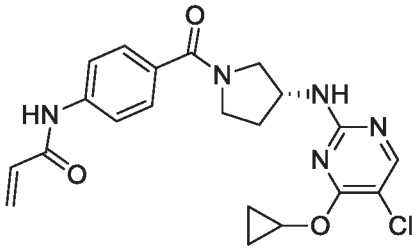
[00284] The title compound was prepared in 18% yield from (R)-5-bromo-N-(pyrrolidin-3-yl)pyrimidin-2-amine according to the procedure for the preparation of (R)-N-(4-(3-((4-cyclopropoxy-5-fluoropyrimidin-2-yl)amino)pyrrolidine-1-carbonyl)phenyl)propionamide. ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.87-2.16 (m, 2H), 3.41-3.80 (m, 4H), 4.23-4.39 (m, 1H), 5.78-5.80 (m, 1H), 6.26-6.48 (m, 2H), 7.49-7.54 (m, 2H), 7.69-7.86 (m, 3H), 8.36-8.43 (m, 2H), 10.33 (s, 1H). Calcd.: 416; Found, 417 ($[M+H]^+$).

Example 20: Synthesis of (R)-N-(4-(3-((5-bromo-4-methoxypyrimidin-2-yl)amino)pyrrolidine-1-carbonyl)phenyl)acrylamide



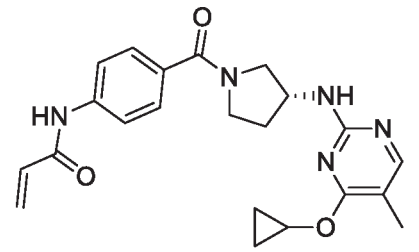
[00285] The title compound was prepared in 10.4% yield from (R)-5-bromo-4-methoxy-N-(pyrrolidin-3-yl)pyrimidin-2-amine according to the procedure for the preparation of (R)-N-(4-(3-((4-cyclopropoxy-5-fluoropyrimidin-2-yl)amino)pyrrolidine-1-carbonyl)phenyl)propionamide. ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.88-2.14 (m, 2H), 3.41-3.93 (m, 7H), 4.26-4.22 (m, 1H), 5.80-5.78 (m, 1H), 6.26-6.30 (m, 1H), 6.41-6.48 (m, 1H), 7.50-7.54 (m, 2H), 7.69-7.74 (m, 3H), 8.14-8.21 (m, 1H), 10.33 (s, 1H). Calcd.: 445; Found, 447 ([M+H]$^+$).

Example 21: Synthesis of (R)-N-(4-(3-((5-chloro-4-cyclopropoxypyrimidin-2-yl)amino)pyrrolidine-1-carbonyl)phenyl)acrylamide



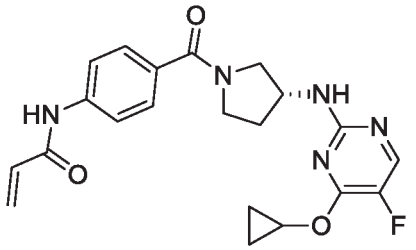
[00286] The title compound was prepared in 23 % yield from (5-Chloro-4-cyclopropoxy-pyrimidin-2-yl)-pyrrolidin-3-yl-amine according to the procedure for the preparation of (R)-N-(4-(3-((4-cyclopropoxy-5-fluoropyrimidin-2-yl)amino)pyrrolidine-1-carbonyl)phenyl)propionamide; ^{1}H NMR (400 MHz, DMSO-d_6): δ 0.68-0.80 (m, 4H), 1.91-2.17 (m, 1H), 2.19-2.21 (m, 1H), 3.38-3.48 (m, 1H), 3.52-3.58 (m, 1H), 3.64-3.68 (m, 1H), 3.77-3.81 (m, 1H), 4.18-4.35 (m, 1H), 4.37-4.41(m, 1H), 5.77-5.80 (m, 1H), 6.26-6.30 (m, 1H), 6.41-6.48 (m, 1H), 7.49-7.54 (m, 2H), 7.69-7.73 (m, 3H), 8.07-8.15(m, 1H), 10.29 (s, 1H). MS Calcd.: 427; Found, 428 ([M+H]$^+$).

Example 22: Synthesis of (R)-N-(4-(3-((4-cyclopropoxy-5-methylpyrimidin-2-yl)amino)pyrrolidine-1-carbonyl)phenyl)acrylamide



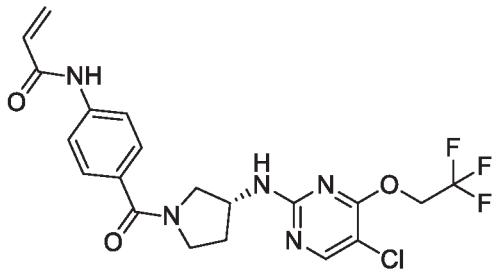
[00287] The title compound was prepared in 21% yield from (R)-4-cyclopropoxy-5-methyl-N-(pyrrolidin-3-yl)pyrimidin-2-amine according to the procedure for the preparation of (R)-N-(4-(3-((4-cyclopropoxy-5-fluoropyrimidin-2-yl)amino)pyrrolidine-1-carbonyl)phenyl)propionamide. ^{1}H NMR (400 MHz, DMSO-d_6): δ 0.52-0.76 (m, 4H), 1.81-1.91 (m, 3H), 1.97-2.15 (m, 2H), 3.36-3.64 (m, 4H), 3.86-4.19 (m, 2H), 5.77-5.80 (m, 1H), 6.26-6.30 (m, 1H), 6.41-6.48 (m, 1H), 7.18 (m, 1H), 7.48-7.54 (m, 2H), 7.68-7.89 (m, 3H), 10.29 (s, 1H). Calcd.: 407; Found, 408 ([M+H]$^+$).

Example 23: Synthesis of (R)-N-(4-(3-((4-cyclopropoxy-5-fluoropyrimidin-2-yl)amino)pyrrolidine-1-carbonyl)phenyl)acrylamide



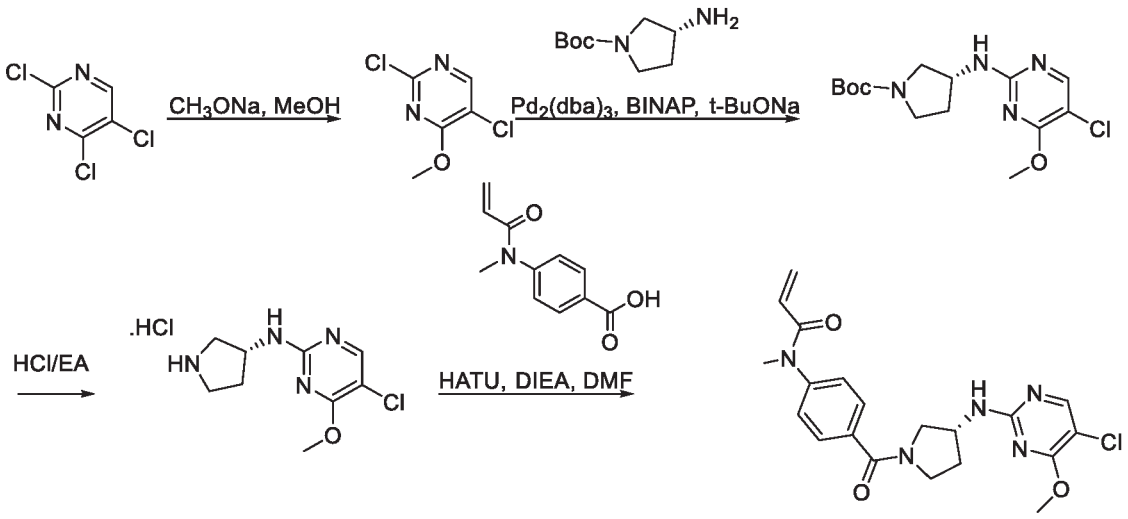
[00288] The title compound was prepared in 20.6% yield from (R)-4-cyclopropoxy-5-fluoro-N-(pyrrolidin-3-yl)pyrimidin-2-amine according to the procedure for the preparation of (R)-N-(4-(3-((4-cyclopropoxy-5-fluoropyrimidin-2-yl)amino)pyrrolidine-1-carbonyl)phenyl)propionamide. ^{1}H NMR (400 MHz, DMSO-d_6): δ 0.62-0.79 (m, 4H), 1.99-2.18 (m, 2H), 3.43-3.86 (m, 4H), 4.19-4.38 (m, 2H), 5.78-5.80 (m, 1H), 6.26-6.31 (m, 1H), 6.42-6.48 (m, 1H), 7.45-7.54 (m, 3H), 7.69-7.74 (m, 2H), 8.06-8.14 (m, 1H), 10.32 (s, 1H). Calcd.: 411; Found, 412 ([M+H]$^+$).

Example 24: Synthesis of (R)-N-(4-(3-((5-chloro-4-(2,2,2-trifluoroethoxy)pyrimidin-2-yl)amino)pyrrolidine-1-carbonyl)phenyl)acrylamide



[00289] The title compound was prepared in 21% yield from [5-chloro-4-(2,2,2-trifluoro-ethoxy)-pyrimidin-2-yl]-pyrrolidin-3-yl-amine according to the procedure for the preparation of (R)-N-(4-(3-((5-chloro-4-(2,2,2-trifluoroethoxy)pyrimidin-2-yl)amino)pyrrolidine-1-carbonyl)phenyl)propionamide. ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.88-2.02 (m, 1H), 2.15-2.18 (m, 1H), 3.39-3.47 (m, 1H), 3.51-3.57 (m, 1H), 3.62-3.71 (m, 1H), 3.75-3.81 (m, 1H), 4.30-4.47 (m, 1H), 5.01-5.13 (m, 2H), 5.78 (d, J = 10.0 Hz, 1H), 6.27-6.32(m, 1H), 6.43-6.50 (m, 1H), 7.50-7.56 (m, 2H), 7.71-7.75 (m, 2H), 7.85-7.97 (m, 1H), 8.22-8.29 (m, 1H), 10.33(s, 1H). MS Calcd.: 469; Found, 470 ([M+H]$^+$).

Example 25: Synthesis of (R)-N-(4-(3-((5-chloro-4-methoxypyrimidin-2-yl)amino)pyrrolidine-1-carbonyl)phenyl)-N-methylacrylamide



Step 1:

[00290] To a solution of 2,4,5-trichloropyrimidine (7.0 g, 38.2 mmol) in MeOH (100 mL) was added sodium methoxide (4.1 g, 76.5 mmol) and the mixture was stirred at RT for 12h. The reaction mixture was evaporated to dryness and the residue purified by silica gel chromatography (Petroleum Ether/Ethyl Acetate = 20/1) to give 2,5-dichloro-4-methoxypyrimidine (5.1 g, 75%). MS Calcd.: 178, MS Found: 179 ($[M+H]^+$).

Step 2:

[00291] To a solution of 2,5-dichloro-4-methoxypyrimidine (2.6 g, 14.5 mmol) in toluene (60 mL) was added (R)-tert-butyl 3-aminopyrrolidine-1-carboxylate (3.0 g, 16.0 mmol), *t*-BuONa (2.1 g, 21.7 mmol), $Pd_2(dba)_3$ (1.7 g, 2.9 mmol) and BINAP (3.6 g, 5.8 mmol) at room temperature under N_2. The mixture was stirred at 100°C for 12h and then concentrated *in vacuo*. The residue was then purified by silica gel chromatography (Petroleum Ether/Ethyl Acetate = 1/1) to afford (R)-tert-butyl 3-((5-chloro-4-methoxypyrimidin-2-yl)amino)pyrrolidine-1-carboxylate (2.4 g, 51%). MS Calcd.: 328, MS Found: 329 ($[M+H]^+$).

Step 3:

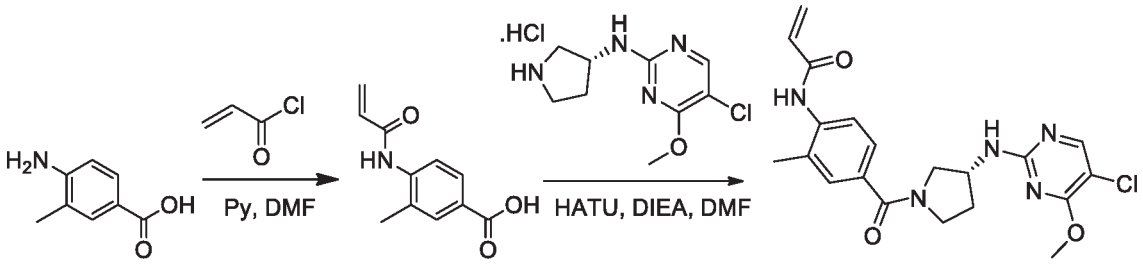
[00292] A solution of (R)-tert-butyl 3-((5-chloro-4-methoxypyrimidin-2-yl)amino)pyrrolidine-1-carboxylate (2.4 g, 7.3 mmol) in HCl/Ethyl Acetate (10 mL, 2.0 M) was stirred at RT for 3h. The reaction mixture was then filtered to give (R)-5-chloro-4-methoxy-N-(pyrrolidin-3-yl)pyrimidin-2-amine hydrochloride (1.7 g, 88%). MS Calcd.: 228, MS Found: 229 ($[M+H]^+$).

Step 4:

[00293] A mixture of (R)-5-chloro-4-methoxy-N-(pyrrolidin-3-yl)pyrimidin-2-amine hydrochloride (129 mg, 0.49 mmol), 4-(N-methylacrylamido)benzoic acid (100 mg, 0.49 mmol), HATU (205 mg, 0.54 mmol) and DIEA (189 mg, 1.47 mmol) in DMF (10 mL) was stirred at 25°C for overnight. The mixture was diluted with H_2O (30 mL) and extracted with DCM (30 mL*2). The combined organic phases were concentrated *in vacuo*. The residue was then purified by *prep*-HPLC to afford (R)-N-

(4-(3-((5-chloro-4-methoxypyrimidin-2-yl)amino)pyrrolidine-1-carbonyl)phenyl)-N-methylacrylamide (58 mg, 29%). ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.80-2.05 (m, 1H), 2.06-2.18 (m, 1H), 3.26 (s, 1.45H), 3.27 (s, 1.55H), 3.35-3.90 (m, 7H), 4.27-4.46 (m, 1H), 5.58-5.62 (m, 1H), 6.11-6.20 (m, 2H), 7.31-7.36 (m, 2H), 7.56-7.69 (m, 3H). 8.08 (m, 0.55H), 8.14 (m, 0.45H). MS Calcd.: 415 Found: 416 ([M+H]$^+$).

Example 26: Synthesis of (R)-N-(4-(3-((5-chloro-4-methoxypyrimidin-2-yl)amino)pyrrolidine-1-carbonyl)-2-methylphenyl)acrylamide



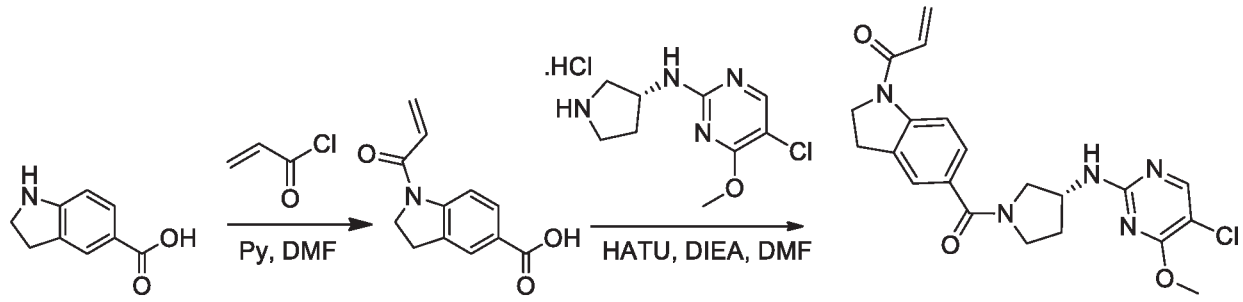
Step 1:

[00294] The title compound was prepared in 29% yield from 4-amino-3-methylbenzoic acid using general procedure of 4-(N-methylacrylamido)benzoic acid. MS Calcd.: 205, MS Found: 206 ([M+H]$^+$).

Step 2 :

[00295] The title compound was prepared in 18% yield from 4-acrylamido-3-methylbenzoic acid using general procedure of (R)-N-(4-(3-((5-chloro-4-methoxypyrimidin-2-yl)amino)pyrrolidine-1-carbonyl)phenyl)-N-methylacrylamide. ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.88-2.02 (m, 1H), 2.09-2.20 (m, 1H), 2.23 (s, 1.65H), 2.25 (s, 1.35H), 3.35-3.94 (m, 7H), 4.24-4.44 (m, 1H), 5.77 (d, J = 10.4 Hz, 1H), 6.26 (d, J = 17.2 Hz, 1H), 6.53-6.60 (m, 1H), 7.31-7.40 (m, 2H), 7.59-7.67 (m, 2H), 8.07 (s, 0.56H), 8.14 (s, 0.44H), 9.51 (s, 1H). MS Calcd.: 415 MS Found: 416 ([M+H]$^+$).

Example 27: Synthesis of (R)-1-(5-(3-((5-chloro-4-methoxypyrimidin-2-yl)amino)pyrrolidine-1-carbonyl)indolin-1-yl)prop-2-en-1-one



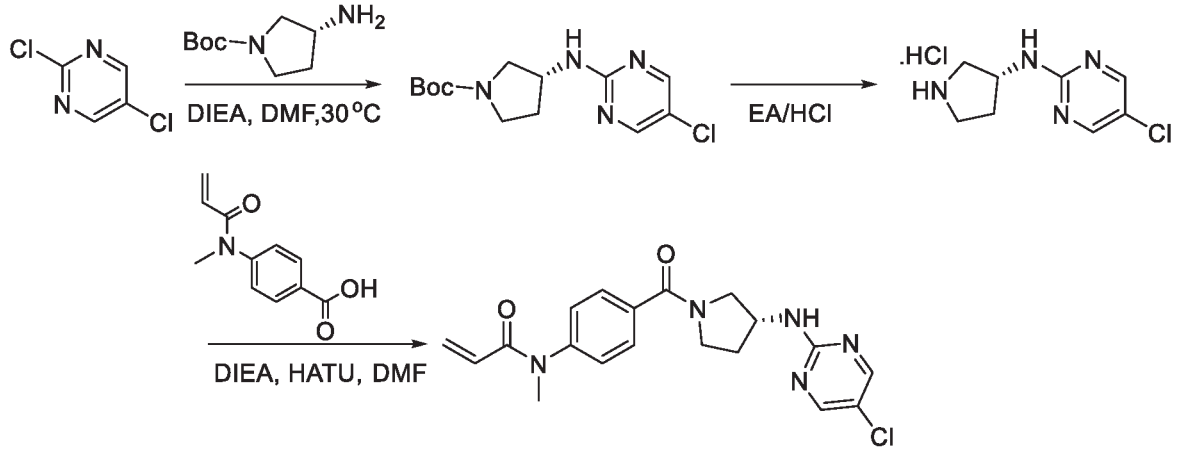
Step 1:

[00296] The title compound was prepared in 42% yield from indoline-5-carboxylic acid using general procedure of 4-(N-methylacrylamido)benzoic acid. MS Calcd.: 217, MS Found: 218 ([M+H]$^+$).

Step 2:

[00297] The title compound was prepared in 10% yield from 1-acryloylindoline-5-carboxylic acid using general procedure of (R)-N-(4-(3-((5-chloro-4-methoxypyrimidin-2-yl)amino)pyrrolidine-1-carbonyl)phenyl)-N-methylacrylamide. ^{1}H NMR (400 MHz, CD_3OD): δ 2.00-2.10 (m, 1H), 2.22-2.33 (m, 1H), 3.22-3.27 (m, 2H), 3.31-4.00 (m, 7H), 4.25-4.55 (m, 3H), 5.85-5.88 (m, 1H), 6.39 (s, 0.43H), 6.43 (s, 0.57H), 6.72-6.79 (m, 1H), 7.34-7.46 (m, 2H), 7.94 (s, 0.52H), 8.00 (s, 0.48H), 8.23 (s, 1H). MS Calcd.: 427 Found: 428 ([M+H]$^+$).

Example 28: Synthesis of (R)-N-(4-(3-((5-chloropyrimidin-2-yl)amino)pyrrolidine-1-carbonyl)phenyl)-N-methylacrylamide



Step 1:

[00298] A mixture of 2,5-dichloropyrimidine (6.1 g, 40.9 mmol), (R)-tert-butyl 3-aminopyrrolidine-1-carboxylate (9.9 g, 53.2 mmol) and DIEA (7.9 g, 61.2 mmol) in DMF (30 mL) was stirred at 30°C for overnight. The reaction was then quenched with water (100 mL) and extracted with DCM (50 mL*3). The combined organic layers were washed with water (100 mL*2) and brine (100 mL), dried over Na_2SO_4, filtered and then concentrated *in vacuo*. The residue was washed with Petroleum Ether to afford (R)-tert-butyl 3-((5-chloropyrimidin-2-yl)amino)pyrrolidine-1-carboxylate (9.9 g, 81%). MS Calcd.: 298, MS Found: 299 ([M+H]$^+$).

Step 2:

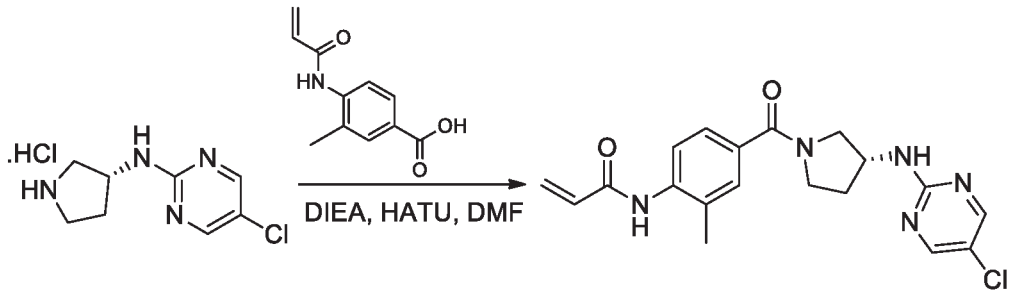
[00299] A solution of (R)-tert-butyl 3-((5-chloropyrimidin-2-yl)amino)pyrrolidine-1-carboxylate (9.9 g, 33.2 mmol) in HCl/Ethyl Acetate (50 mL, 2.0 M) was stirred at RT for 3h. The reaction mixture was filtered to afford (R)-5-chloro-N-(pyrrolidin-3-yl)pyrimidin-2-amine hydrochloride (6.9 g, 89%). MS Calcd.: 198, MS Found: 199 ([M+H]+)

Step 3:

[00300] The title compound was prepared in 48% yield from 4-(N-methylacrylamido)benzoic acid using general procedure of (R)-N-(4-(3-((5-chloro-4-methoxypyrimidin-2-yl)amino)pyrrolidine-1-carbonyl)phenyl)-N-methylacrylamide. ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.87-2.03 (m, 1H), 110-

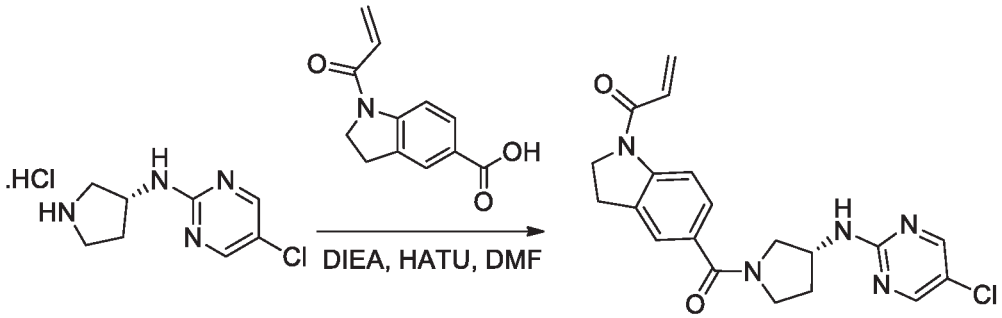
2.20 (m, 1H), 3.26-3.27 (m, 3H), 3.33-3.81 (m, 4H), 4.25-4.44 (m, 1H), 5.58-5.61 (m, 1H), 6.09-6.19 (m, 2H), 7.31-7.36 (m, 2H), 7.56-7.61 (m, 2H), 7.81-7.84 (m, 1H), 8.32 (s, 1H), 8.38 (s, 1H). MS Calcd.: 385 Found: 386 ([M+H]$^+$).

Example 29: Synthesis of (R)-N-(4-(3-((5-chloropyrimidin-2-yl)amino)pyrrolidine-1-carbonyl)-2-methylphenyl)acrylamide



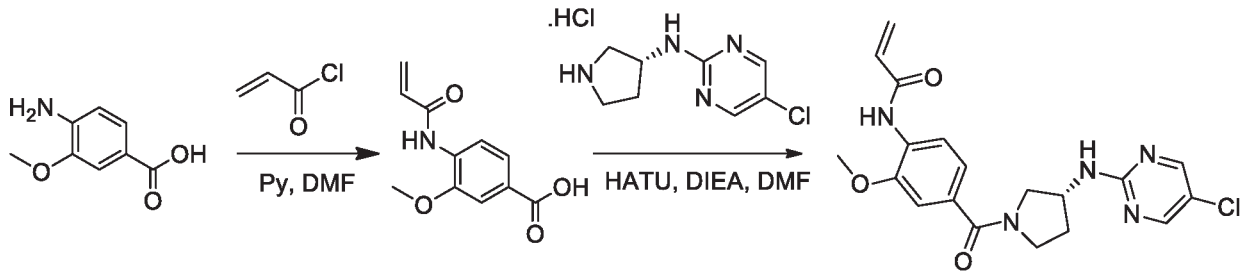
[00301] The title compound was prepared in 43% yield from 4-acrylamido-3-methylbenzoic acid using general procedure of (R)-N-(4-(3-((5-chloro-4-methoxypyrimidin-2-yl)amino)pyrrolidine-1-carbonyl)phenyl)-N-methylacrylamide. ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.86-2.01 (m, 1H), 2.10-2.19 (m, 1H), 2.23 (s, 1.65H), 2.25 (s, 1.35H), 3.28-3.78 (m, 4H), 4.22-4.42 (m, 1H), 5.77 (d, J = 10.0 Hz, 1H), 6.26 (d, J = 17.2 Hz, 1H), 6.53-6.60 (m, 1H), 7.30-7.40 (m, 2H), 7.59-7.64 (m, 1H), 7.79-7.82 (m, 1H), 8.32 (s, 1H), 8.38 (s, 1H), 9.51 (s, 1H). MS Calcd.: 385 MS Found: 386 ([M+H]$^+$).

Example 30: Synthesis of (R)-1-(5-(3-((5-chloropyrimidin-2-yl)amino)pyrrolidine-1-carbonyl)indolin-1-yl)prop-2-en-1-one



[00302] The title compound was prepared in 5% yield from (R)-5-chloro-N-(pyrrolidin-3-yl)pyrimidin-2-amine hydrochloride using general procedure of (R)-1-(5-(3-((5-chloropyrimidin-2-yl)amino)pyrrolidine-1-carbonyl)indolin-1-yl)prop-2-en-1-one. ^{1}H NMR (400 MHz, CD_3OD): δ 2.00-2.10 (m, 1H), 2.22-2.33 (m, 1H), 3.24-3.31 (m, 2H), 3.44-3.94 (m, 4H), 4.25-4.55 (m, 3H), 5.85-5.88 (m, 1H), 6.39 (s, 0.44H), 6.43 (s, 0.57H), 6.73-6.79 (m, 1H), 7.35-7.45 (m, 2H), 8.21-8.23 (m, 3H). MS Calcd.: 397 Found: 398 ([M+H]+).

Example 31: Synthesis of (R)-N-(4-(3-((5-chloropyrimidin-2-yl)amino)pyrrolidine-1-carbonyl)-2-methoxyphenyl)acrylamide



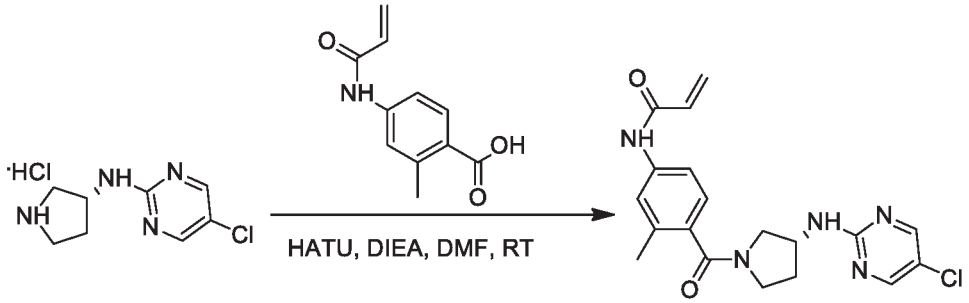
Step 1:

[00303] The title compound was prepared in 30% yield from 4-amino-3-methoxybenzoic acid using general procedure of 4-(N-methoxyacrylamido)benzoic acid. MS Calcd.: 221, MS Found: 222 ($[M+H]^+$).

Step 2 :

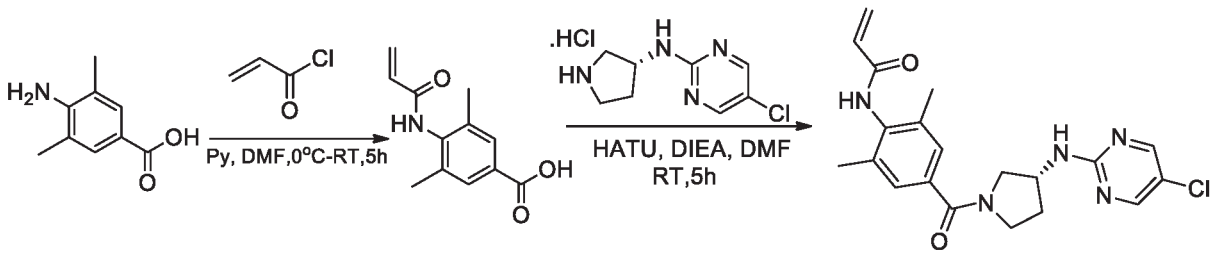
[00304] The title compound was prepared in 15% yield from4-acrylamido-3-methoxybenzoic acid using general procedure of (R)-N-(4-(3-((5-chloropyrimidin-2-yl)amino)pyrrolidine-1-carbonyl)-2-methoxyphenyl)acrylamide. ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.88-2.08 (m, 1H), 2.14-2.16 (m, 1H), 3.35-3.89 (m, 7H), 4.24-4.45 (m, 1H), 5.74 (d, J = 10.4 Hz, 1H), 6.27 (d, J = 16.8 Hz, 1H), 6.69-6.76 (m, 1H), 7.07-7.19 (m, 2H), 7.79-7.83 (m, 1H), 8.11 (s, 0.56H), 8.14 (s, 0.44H), 8.32-8.38 (m, 2H), 9.47(s, 1H). MS Calcd.: 401 MS Found: 402 ($[M+H]^+$).

Example 32: Synthesis of (R)-N-(4-(3-((5-chloropyrimidin-2-yl)amino)pyrrolidine-1-carbonyl)-3-methylphenyl)acrylamide



[00305] The title compound was prepared in 35% yield from (R)-5-chloro-N-(pyrrolidin-3-yl)pyrimidin-2-amine hydrochloride using general procedure of (R)-N-(4-(3-((5-chloropyrimidin-2-yl)amino)pyrrolidine-1-carbonyl)-3-methylphenyl)acrylamide. ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.88-1.98 (m, 1H), 2.07-2.22 (m, 4H), 3.07-3.16 (m, 1H), 3.42-3.51 (m, 2H), 3.68-3.77 (m, 1H), 4.23-4.37 (m, 1H), 5.74-5.77 (m, 1H), 6.23-6.28 (m, 1H), 6.38-6.43 (m, 1H), 7.12-7.20 (m, 1H), 7.49-7.54 (m, 1H),7.76-7.83(m, 1H), 8.31 (s, 1H), 8.38 (s, 1H), 10.14-10.16 (m, 1H). MS Calcd.: 385 Found: 386 ($[M+H]^+$).

Example 33: Synthesis of (R)-N-(4-(3-((5-chloropyrimidin-2-yl)amino)pyrrolidine-1-carbonyl)-2,6-dimethylphenyl)acrylamide



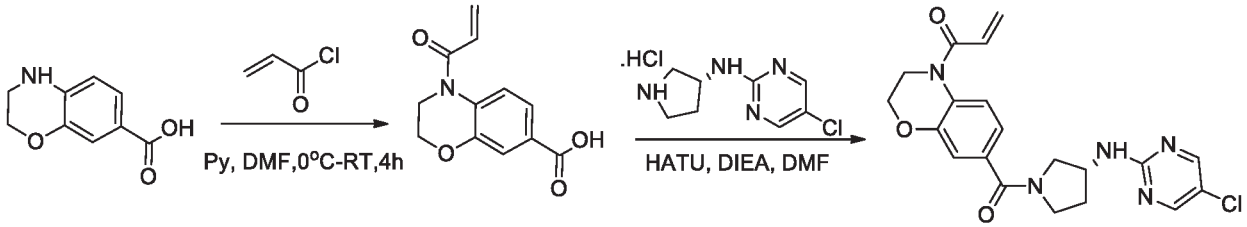
Step 1:

[00306] The title compound was prepared in 31% yield from 4-amino-3,5-dimethylbenzoic acid using general procedure of 4-(N-methoxyacrylamido)benzoic acid. MS Calcd.: 219, MS Found: 220 ($[M+H]^+$)

Step 2:

[00307] The title compound was prepared in 25% yield from 4-amino-3,5-dimethylbenzoic acid using general procedure of N-{4-[3-(5-Chloro-pyrimidin-2-ylamino)-pyrrolidine-1-carbonyl]-2,6-dimethyl-phenyl}-acrylamide. ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.87-1.99 (m, 1H), 2.13-2.19 (m, 7H), 3.41-3.52 (m, 2H), 3.67-3.78 (m, 2H), 4.22-4.40 (m, 1H), 5.75 (d, J = 10.4 Hz, 1H), 6.22 (d, J = 17.2 Hz, 1H), 6.48-6.51 (m, 1H), 7.19 (s, 1H), 7.24 (s, 1H), 7.79-7.82 (m, 1H), 8.33 (s, 1H), 8.38 (s, 1H), 9.54 (d, J = 3.6 Hz, 1H). MS Calcd.: 399 MS Found: 400 ($[M+H]^+$).

Example 34: Synthesis of (R)-1-(7-(3-((5-chloropyrimidin-2-yl)amino)pyrrolidine-1-carbonyl)-2H-benzo[b][1,4]oxazin-4(3H)-yl)prop-2-en-1-one



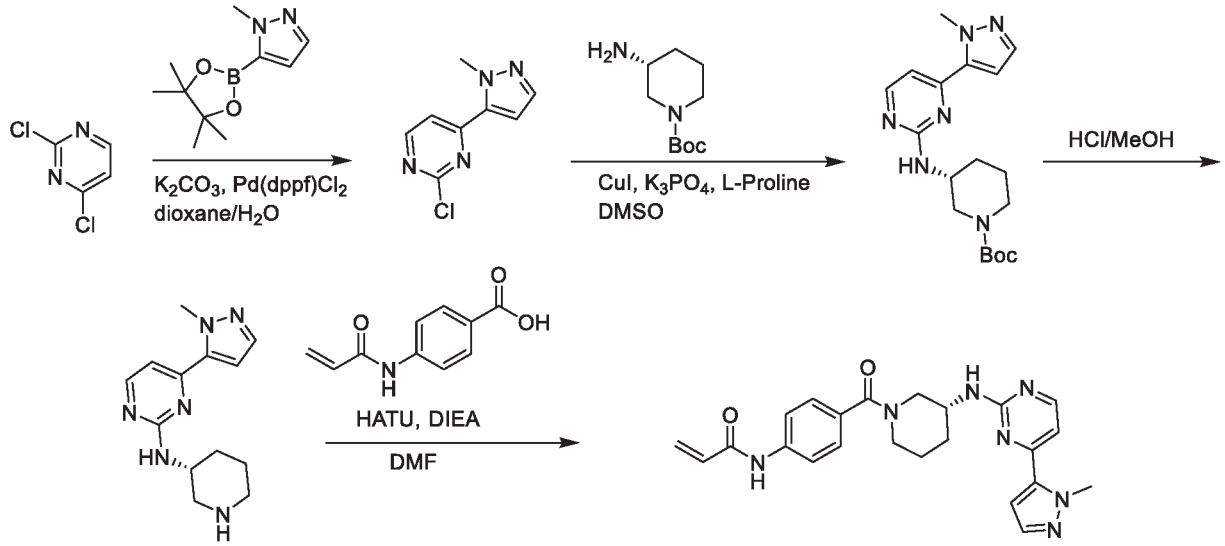
Step 1:

[00308] The title compound was prepared in 44% yield from 3,4-dihydro-2H-benzo[b][1,4]oxazine-7-carboxylic acid using general procedure of 4-(N-methoxyacrylamido)benzoic acid MS Calcd.: 233, MS Found: 234 ($[M+H]^+$)

Step 2:

[00309] The title compound was prepared in 8% yield from 4-acryloyl-3,4-dihydro-2H-benzo[b][1,4]oxazine-7-carboxylic acid using general procedure of N-{4-[3-(5-chloro-pyrimidin-2-ylamino)-pyrrolidine-1-carbonyl]-2,6-dimethyl-phenyl}-acrylamide. ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.86-2.13 (m, 2H), 3.34 (m, 2H), 3.64 (m, 2H), 3.95 (m, 2H), 4.31-4.40 (m, 3H), 5.82-5.85 (m, 1H), 6.25-6.30 (m, 1H), 6.782 (m, 1H), 7.02-7.07 (m, 2H), 7.49 (m, 1H), 7.81 (m, 1H), 8.32-8.38 (m, 2H). MS Calcd.: 413 MS Found: 414 ($[M+H]^+$).

Example 35: Synthesis of (R)-N-(4-(3-((4-(1-methyl-1H-pyrazol-5-yl)pyrimidin-2-yl)amino)piperidine-1-carbonyl)phenyl)acrylamide



Step 1:

[00310] A mixture of 2,4-dichloropyrimidine (1.04 g, 7 mmol), 1-methyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole (1.46 g, 7 mmol), K_2CO_3 (1.93 g, 14 mmol) and $Pd(dppf)Cl_2$ (512 mg, 0.7 mmol) in Dioxane/H_2O (20 mL/5 mL) was stirred at 120°C for 2 hours. The mixture was concentrated in-vacuo and the residue was purified by flash chromatography on silica gel (Petroleum Ether/Ethyl Acetate = 2/1) to afford 2-chloro-4-(1-methyl-1H-pyrazol-5-yl)pyrimidine (1.3 g, 96%). ^1H NMR (400 MHz, $CDCl_3$): δ 4.33 (s, 3H), 6.82 (d, J = 2.0 Hz, 1H), 7.48 (d, J = 5.2 Hz, 1H), 7.55 (d, J = 2.0 Hz, 1H), 8.63 (d, J = 5.2 Hz, 1H).

Step 2:

[00311] A mixture of 2-chloro-4-(1-methyl-1H-pyrazol-5-yl)pyrimidine (600 mg, 3.1 mmol), (R)-tert-butyl 3-aminopiperidine-1-carboxylate (619 mg, 3.1 mmol), CuI (285 mg, 1.5 mmol), K_3PO_4 (1.3 g, 6.2 mmol) and L-Proline (356 mg, 3.1 mmol) in DMSO (10 mL) was stirred at 35°C for overnight. To the mixture was then added H_2O (50 mL) and extracted with EtOAc (50 mL*2). The combined organic layers were washed with $NH_3.H_2O$ (50 mL*2, 1M) and concentrated in-vacuo. The residue was purified by column ACN/H_2O (5-95%) to afford (R)-tert-butyl 3-((4-(1-methyl-1H-pyrazol-5-yl)pyrimidin-2-yl)amino)piperidine-1-carboxylate (180 mg, 16%). MS Calcd.: 358 Found: 359 ([M+H]+).

Step 3:

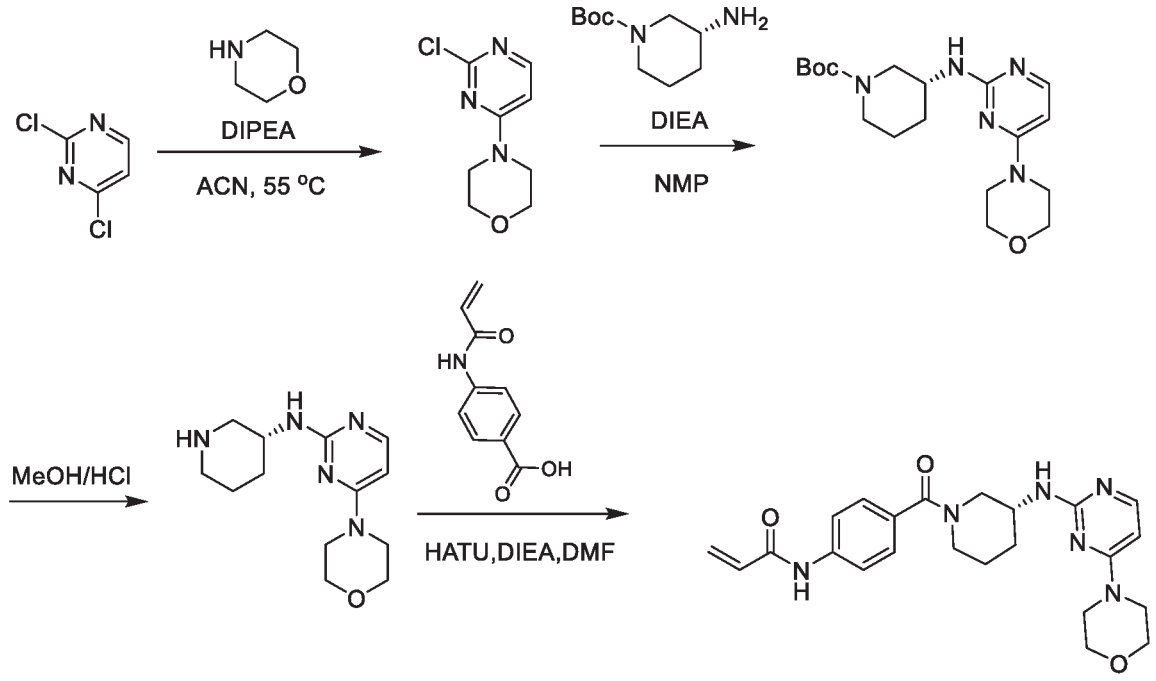
[00312] To a solution of (R)-tert-butyl 3-((4-(1-methyl-1H-pyrazol-5-yl)pyrimidin-2-yl)amino)piperidine-1-carboxylate (180 mg, 0.5 mmol) in MeOH (1 mL) was added HCl/MeOH (1mL, 1M) and then stirred at room temperature for 2 hours. The reaction mixture was concentrated to afford (R)-4-(1-

methyl-1H-pyrazol-5-yl)-N-(piperidin-3-yl)pyrimidin-2-amine (130 mg, 100%). MS Calcd.: 258 Found: 259 ($[M+H]^+$).

Step 4:

[00313] A mixture of (R)-4-(1-methyl-1H-pyrazol-5-yl)-N-(piperidin-3-yl)pyrimidin-2-amine (130 mg, 0.5 mmol), 4-acrylamidobenzoic acid (105 mg, 0.55 mmol), HATU (228 mg, 0.6 mmol) and DIPEA (258 mg, 2 mmol) in DMF (2 mL) was stirred at 25°C for overnight. The reaction mixture was then diluted with H_2O (30 mL), extracted with Ethyl Acetate (30 mL*2), and the combined organic layers were concentrated in vacuo. The residue was purified by prep-TLC (DCM/MeOH = 20/1) to afford (R)-N-(4-(3-((4-(1-methyl-1H-pyrazol-5-yl)pyrimidin-2-yl)amino)piperidine-1-carbonyl)phenyl)acrylamide (26 mg, 12%). ^{1}H NMR (400 MHz, CD_3OD): δ 1.67-2.12 (m, 4H), 3.10-3.33 (m, 1H), 3.47-4.36 (m, 7H), 5.76-5.80 (m, 1H), 6.37 (s, 2H), 6.59-6.86 (m, 2H), 6.95-7.79 (m, 5H), 8.21-8.33 (m, 1H). MS Calcd.: 431 Found: 432 ($[M+H]^+$).

Example 36: (R)-N-(4-(3-((4-morpholinopyrimidin-2-yl)amino)piperidine-1-carbonyl)phenyl)acrylamide



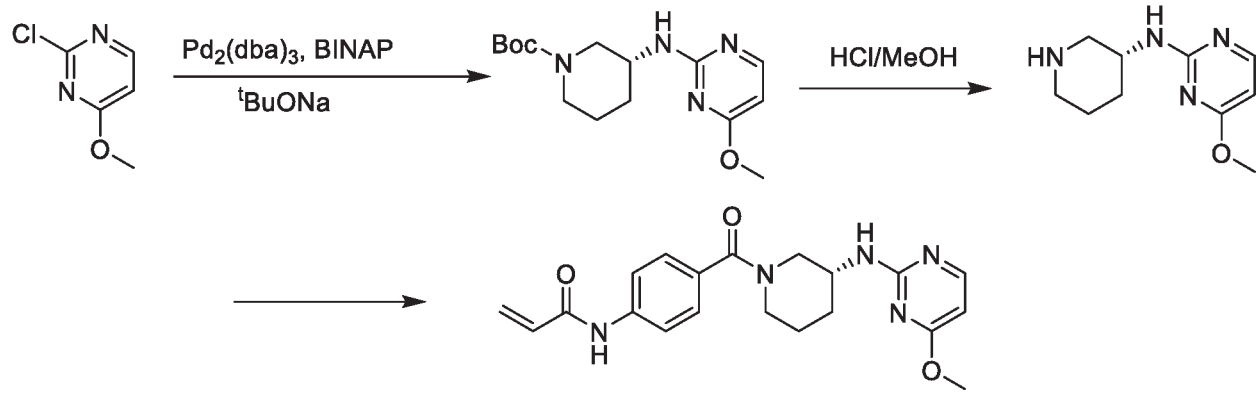
Step 1:

[00314] A mixture of 2,4-dichloropyrimidine (500 mg, 3.35 mmol), morpholine (292 mg, 3.35 mmol) and DIPEA (1.3 g, 10.05 mmol) in ACN (3 mL) was stirred at 55°C for 2 hours. The mixture was then concentrated in-vacuo and purified by flash chromatography on silica gel (Petroleum Ether/Ethyl Acetate = 2/1) to afford 4-(2-chloropyrimidin-4-yl)morpholine (660 mg, 98%) as a white solid. ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.66 (br s, 4H), 3.77-3.80 (m, 4H), 6.38-6.41 (m, 1H), 8.07-8.10 (m, 1H).

Step 2 to 4

[00315] The title compound was prepared in 11% yield from (R)-tert-butyl 3-((4-morpholinopyrimidin-2-yl)amino)piperidine-1-carboxylate using general procedure of (R)-N-(4-(3-((4-(1-methyl-1H-pyrazol-5-yl)pyrimidin-2-yl)amino)piperidine-1-carbonyl)phenyl)acrylamide. ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.47-1.94 (m, 4H), 2.50-3.04 (m, 1H), 3.45-3.83 (m, 11H), 4.28-4.42 (m, 1H), 5.78-5.80 (m, 1H), 6.06-6.09 (m, 1H), 6.26-6.30 (m, 1H), 6.41-6.48 (m, 1H), 7.24-7.40 (m, 2H), 7.59-7.80 (m, 4H), 10.30 (br s, 1H). MS Calcd.: 436 MS Found: 437 ([M+H]$^+$).

Example 37: Synthesis of (R)-N-(4-(3-((4-methoxypyrimidin-2-yl)amino)piperidine-1-carbonyl)phenyl)acrylamide



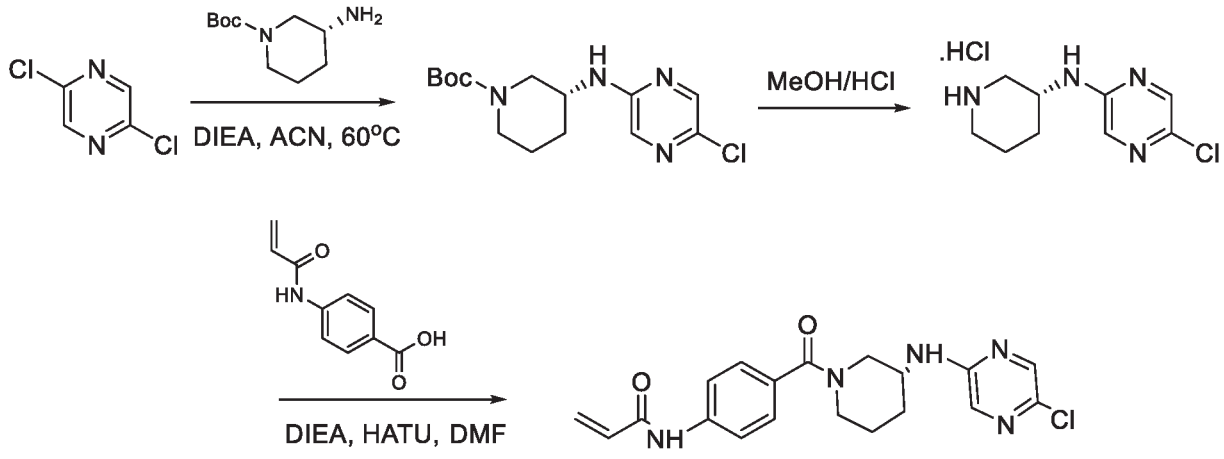
Step 1:

[00316] A mixture of 2-chloro-4-methoxypyrimidine (144 mg, 1 mmol), (R)-tert-butyl 3-aminopiperidine-1-carboxylate (200 mg, 1 mmol), tBuONa (144 mg g, 1.5 mmol), $Pd_2(dba)_3$ (183 mg, 0.2 mmol) and BINAP (249 mg, 0.4 mmol) in 4 mL of toluene was stirred at 50°C for 3 hours. The mixture was diluted with 10 mL of water and extracted with Ethyl Acetate (10 mL*2). The combined organic layers were dried over Na_2SO_4, filtered and concentrated *in vacuo*. The residue was purified by flash chromatography on silica gel (Petroleum ether/Ethyl Acetate = 2/1) to afford (R)-tert-butyl 3-((4-methoxypyrimidin-2-yl)amino)piperidine-1-carboxylate (1.3 g, 29%). [M+H] MS Calcd.: 381 Found: 382 ([M+H]$^+$).

Step 2 to Step 3:

[00317] The title compound was prepared in 4% yield from (R)-4-methoxy-N-(piperidin-3-yl)pyrimidin-2-amine using general procedure of (R)-N-(4-(3-((4-(1-methyl-1H-pyrazol-5-yl)pyrimidin-2-yl)amino)piperidine-1-carbonyl)phenyl)acrylamide. ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.25-1.31 (m, 2H), 1.47-1.64 (m, 1H), 1.81-1.98 (m, 1H), 2.94-3.22 (m, 2H), 3.52-3.86 (m, 6H), 5.77-5.83 (m, 1H), 6.27-6.54 (m, 2H), 6.80-6.83 (m, 1H), 7.319-7.407 (m, 2H), 7.64-7.75 (m, 2H), 7.99-8.08 (m, 2H), 10.31-10.32 (m, 1H). MS Calcd.: 381 Found: 382 ([M+H]$^+$).

Example 38: Synthesis of (R)-N-(4-(3-((5-chloropyrazin-2-yl)amino)piperidine-1-carbonyl)phenyl)acrylamide



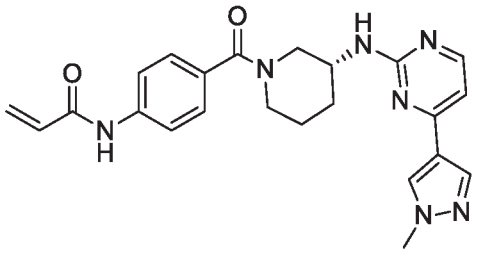
Step 1:

[00318] A mixture of 2,5-dichloropyrazine (367 mg, 2.5 mmol), (R)-tert-butyl 3-aminopiperidine-1-carboxylate (500 mg, 2.5 mmol) and DIEA (645 mg, 5mmol) in ACN (5 mL) was stirred at 60°C for overnight. After cooling to room temperature, the reaction mixture was concentrated and purified by silica gel chromatography (Petroleum Ether/Ethyl Acetate = 1/1) to afford (R)-tert-butyl 3-((5-chloropyrazin-2-yl)amino)piperidine-1-carboxylate (530 mg, 68%). MS Calcd.: 312, MS Found: 313 ($[M+H]^+$).

Step 2 to 3:

[00319] The title compound was prepared in 21% yield from(R)-5-chloro-N-(piperidin-3-yl)pyrazin-2-amine hydrochloride using general procedure of (R)-N-(4-(3-((4-(1-methyl-1H-pyrazol-5-yl)pyrimidin-2-yl)amino)piperidine-1-carbonyl)phenyl)acrylamide. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.73-2.05 (m, 4H), 3.18-4.22 (m, 5H), 5.08-5.70 (m, 1H), 5.79 (d, J = 10.0 Hz, 1H), 6.26-6.30 (m, 1H), 6.43-6.48 (m, 1H), 7.37-7.57 (m, 4H), 7.80 (s, 1H), 8.17-8.43 (m, 1H). MS Calcd.: 385 MS Found: 386 ($[M+H]^+$).

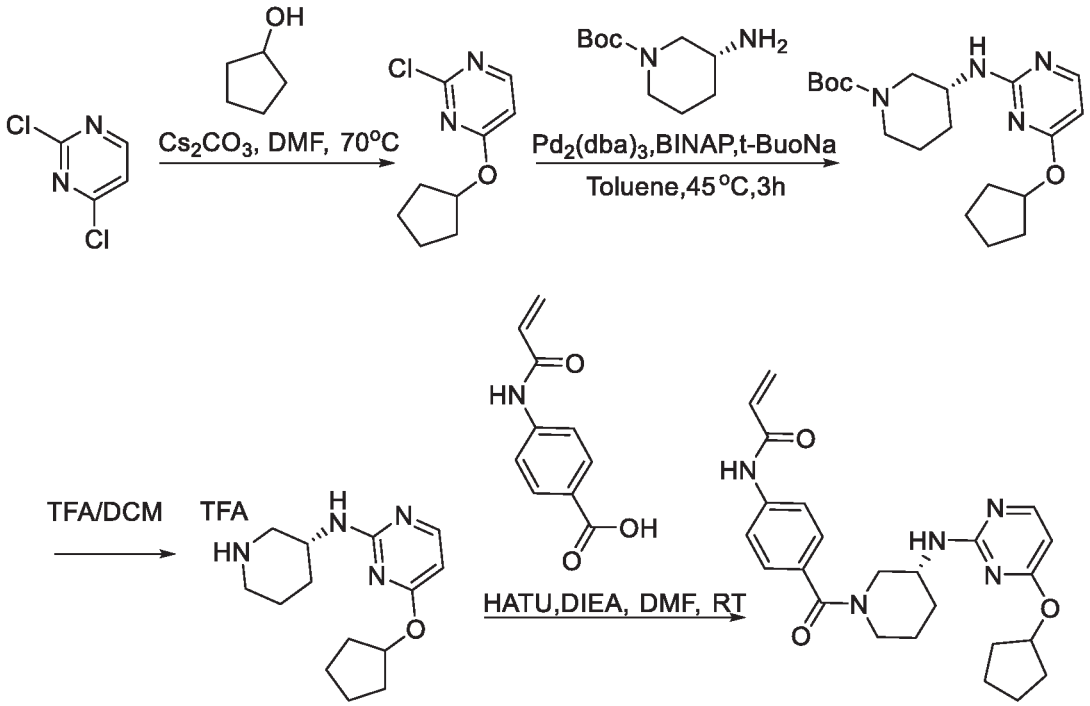
Example 39: Synthesis of (R)-N-(4-(3-((4-(1-methyl-1H-pyrazol-4-yl)pyrimidin-2-yl)amino)piperidine-1-carbonyl)phenyl)acrylamide



[00320] The title compound was prepared in 21% yield from 4-(1-methyl-1H-pyrazol-4-yl)-N-(piperidin-3-yl)pyrimidin-2-amine using general procedure of (R)-N-(4-(3-((4-(1-methyl-1H-pyrazol-5-

yl)pyrimidin-2-yl)amino)piperidine-1-carbonyl)phenyl)acrylamide. 1H NMR (400 MHz, DMSO-d_6): δ1.47-1.67 (m, 2H), 1.78-1.88 (m, 1H), 1.96-2.03 (m, 1H), 2.78-3.16 (m, 2H), 3.67-4.15 (m, 6H), 5.74-5.82 (m, 1H), 6.22-6.49 (m, 2H), 6.79-6.87 (m, 1H), 7.07-8.32 (m, 8H), 10.13-10.46 (m, 1H). MS Calcd.: 431 MS Found: 432 ([M+H]$^+$).

Example 40: Synthesis of (R)-N-(4-(3-((4-(cyclopentyloxy)pyrimidin-2-yl)amino)piperidine-1-carbonyl)phenyl)acrylamide



Step 1:

[00321] To a solution of 2,4-dichloropyrimidine (2.0 g, 13.40 mmol) in DMF (50 mL) was added cyclopentanol (1.5 mL, 16.10 mmol) and cesium carbonate (8.8 g, 26.84 mmol) at room temperature. The mixture was then heated to 80°C for 1h followed by stirring at 70°C for 16h. The reaction mixture was then cooled to RT, quenched with water (100 mL), and extracted with Ethyl Acetate (50 mL*3). The combined organic layers were washed with water (100 mL*2) and brine (100 mL), dried over Na_2SO_4, filtered and then concentrated *in vacuo*. The residue was purified by silica gel chromatography (Petroleum Ether/Ethyl Acetate = 1/1) to give 2-chloro-4-(cyclopentyloxy)pyrimidine (1.2 g, 46%). MS Calcd.: 198, MS Found: 199 ([M+H]$^+$).

Step 2:

[00322] To a solution of 2-chloro-4-(cyclopentyloxy)pyrimidine (1.1 g, 5.55 mmol) in toluene (12 mL) was added (R)-tert-butyl 3-aminopiperidine-1-carboxylate (1.1 g, 5.55 mmol), *t*-BuONa (800 mg, 8.33mmol), $Pd_2(dba)_3$ (638 mg, 1.11 mmol) and BINAP (1.38 g, 2.22 mmol) at room temperature. This mixture was stirred at 45°C for 3h. The reaction was filtered and concentrated in-vacuo. The residue was purified by silica gel chromatography (Petroleum Ether/Ethyl Acetate = 1/1) to afford

(R)-tert-butyl 3-((4-(cyclopentyloxy)pyrimidin-2-yl)amino)piperidine-1-carboxylate (275 mg, 14%). MS Calcd.: 362, MS Found: 363 ([M+H]$^+$).

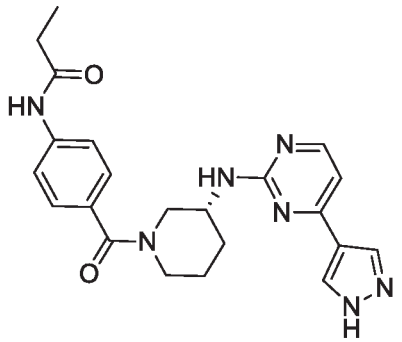
Step 3:

[00323] A solution of (R)-tert-butyl 3-((4-(cyclopentyloxy)pyrimidin-2-yl)amino)piperidine-1-carboxylate (275 mg, 0.76 mmol) in DCM (15 mL) and TFA (5 mL) was stirred at rt for 2h. The reaction mixture was concentrated to give the crude (R)-4-(cyclopentyloxy)-N-(piperidin-3-yl)pyrimidin-2-amine (286 mg, 100%). MS Calcd.: 262, MS Found: 263 ([M+H]$^+$).

Step 4:

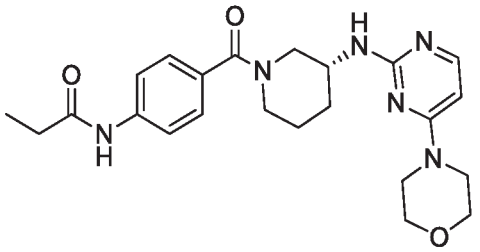
[00324] To a solution of (R)-4-(cyclopentyloxy)-N-(piperidin-3-yl)pyrimidin-2-amine (280 mg, 0.74 mmol), 4-acrylamidobenzoic acid (156 mg, 0.82 mmol) and DIEA (0.36 mL, 2.23 mmol) in DMF (15 mL) was added HATU (340 mg, 0.89 mmol) at rt. The reaction mixture was stirred at rt for 12h. The reaction was concentrated. The residue was purified by *prep*-HPLC to give (R)-N-(4-(3-((4-(cyclopentyloxy)pyrimidin-2-yl)amino)piperidine-1-carbonyl)phenyl)acrylamide (127 mg, 39%). ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.53-1.64 (m, 8H), 1.82-1.92 (m, 4H), 2.51-2.62 (m, 1H), 3.29-3.32 (m, 3H), 4.51-4.62 (m, 1H), 5.32-5.42 (m, 1H), 5.76-5.79 (m, 1H), 5.92 (br s, 1H), 6.25 (d, J = 2.0 Hz, 1H), 6.43-6.47 (m, 1H), 7.02-7.08 (m, 1H), 7.33-7.34 (m, 1H), 7.61-7.64 (m, 2H), 7.93 (m, 1H), 10.25 (s, 1H). MS Calcd.: 435, MS Found: 436 ([M+H]$^+$).

Example 41: Synthesis of (R)-N-(4-(3-((4-(1H-pyrazol-4-yl)pyrimidin-2-yl)amino)piperidine-1-carbonyl)phenyl)propionamide



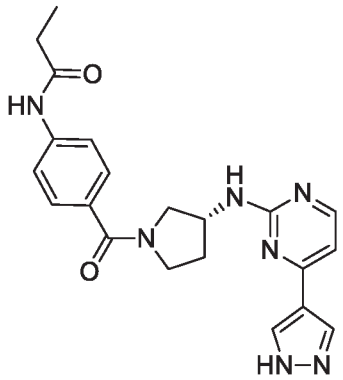
[00325] The title compound was prepared in 3% yield from (R)-N-(piperidin-3-yl)-4-(1H-pyrazol-4-yl)pyrimidin-2-amine using general procedure of (R)-N-(4-(3-((4-(1-methyl-1H-pyrazol-5-yl)pyrimidin-2-yl)amino)piperidine-1-carbonyl)phenyl)acrylamide. ^{1}H NMR (400 MHz, CD_3OD): δ 1.5 (s, 3H), 1.71-1.84 (m, 2H), 1.98-2.11 (m, 2H), 2.36 (s, 2H), 3.05-3.20 (m, 1H), 3.72-3.90 (m, 4H), 6.71-6.85 (m, 1H), 7.25-7.41 (m, 4H) , 7.99-8.19 (m, 3H). MS Calcd.: 419 MS Found: 420 ([M+H]$^+$).

Example 42: Synthesis of (R)-N-(4-(3-((4-morpholinopyrimidin-2-yl)amino)piperidine-1-carbonyl)phenyl)propionamide



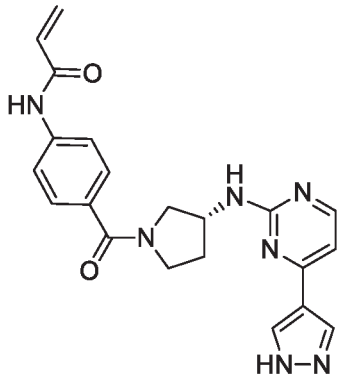
[00326] The title compound was prepared in 4% yield from (R)-4-morpholino-N-(piperidin-3-yl)pyrimidin-2-amine using general procedure of (R)-N-(4-(3-((4-(1-methyl-1H-pyrazol-5-yl)pyrimidin-2-yl)amino)piperidine-1-carbonyl)phenyl)acrylamide. ^{1}H NMR (400 MHz, CD_3OD): δ 1.18-1.22 (m, 3H), 1.28-1.32 (m, 1H), 1.59-2.07 (m, 4H), 2.37-2.43 (m, 2H), 3.35-3.47 (m, 3H), 3.59-3.65 (m, 7H), 3.94-4.50 (m, 2H), 6.10-6.14 (m, 1H), 7.15-7.16 (m, 1H), 7.41-7.49 (m, 2H), 7.67-7.75 (m, 2H). MS Calcd.: 438 MS Found: 439 ($[M+H]^+$).

Example 43: Synthesis of (R)-N-(4-(3-(4-(1H-pyrazol-4-yl)pyrimidin-2-yl)pyrrolidine-1-carbonyl)phenyl)propionamide



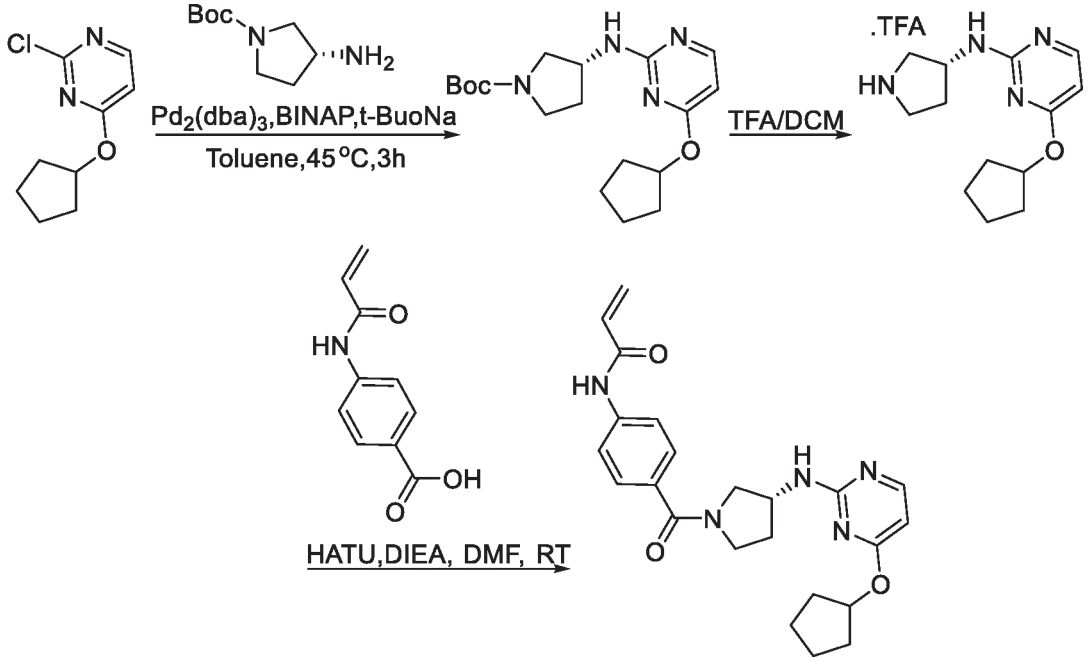
[00327] The title compound was prepared in 1% yield from (R)-4-(1H-pyrazol-4-yl)-2-(pyrrolidin-3-yl)pyrimidine using general procedure of (R)-N-(4-(3-((4-(1-methyl-1H-pyrazol-5-yl)pyrimidin-2-yl)amino)piperidine-1-carbonyl)phenyl)acrylamide. ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.07-1.11 (m, 3H), 1.88-2.37 (m, 4H), 3.43-3.82 (m, 4H), 4.34-4.51 (m, 1H), 6.87-6.94 (m, 1H), 7.33-7.67 (m, 5H), 8.16-8.25 (m, 3H), 10.03-10.06 (m, 1H), 13.17-13.20 (m, 1H). MS Calcd.: 405 MS Found: 406 ($[M+H]^+$).

Example 44: Synthesis of (R)-N-(4-(3-((4-(1H-pyrazol-4-yl)pyrimidin-2-yl)amino)pyrrolidine-1-carbonyl)phenyl)acrylamide



[00328] The title compound was prepared in 5% yield from (R)-4-(1H-pyrazol-4-yl)-N-(pyrrolidin-3-yl)pyrimidin-2-amine hydrochloride using general procedure of (R)-N-(4-(3-((4-(1-methyl-1H-pyrazol-5-yl)pyrimidin-2-yl)amino)piperidine-1-carbonyl)phenyl)acrylamide. ^{1}H NMR (400 MHz, CD_3OD): δ 2.03-2.38 (m, 2H), 3.49-4.02 (m, 4H), 4.41-4.66 (m, 2H), 5.76-5.81 (m, 1H), 6.36-6.46 (m, 2H), 6.87-6.94 (m, 1H), 7.52-7.77 (m, 4H), 8.09-8.22 (m, 3H). MS Calcd.: 403 MS Found: 404 ($[M+H]^+$).

Example 45: Synthesis of N-{4-[3-(4-Cyclopentyloxy-pyrimidin-2-ylamino)-pyrrolidine-1-carbonyl]-phenyl}-acrylamide



Step 1:

[00329] The title compound was prepared in 12% yield from 2-chloro-4-(cyclopentyloxy)pyrimidine using general procedure of 3-(4-cyclopentyloxy-pyrimidin-2-ylamino)-piperidine-1-carboxylic acid tert-butyl ester. MS Calcd.: 348.1, MS Found: 349.1 ($[M+H]^+$).

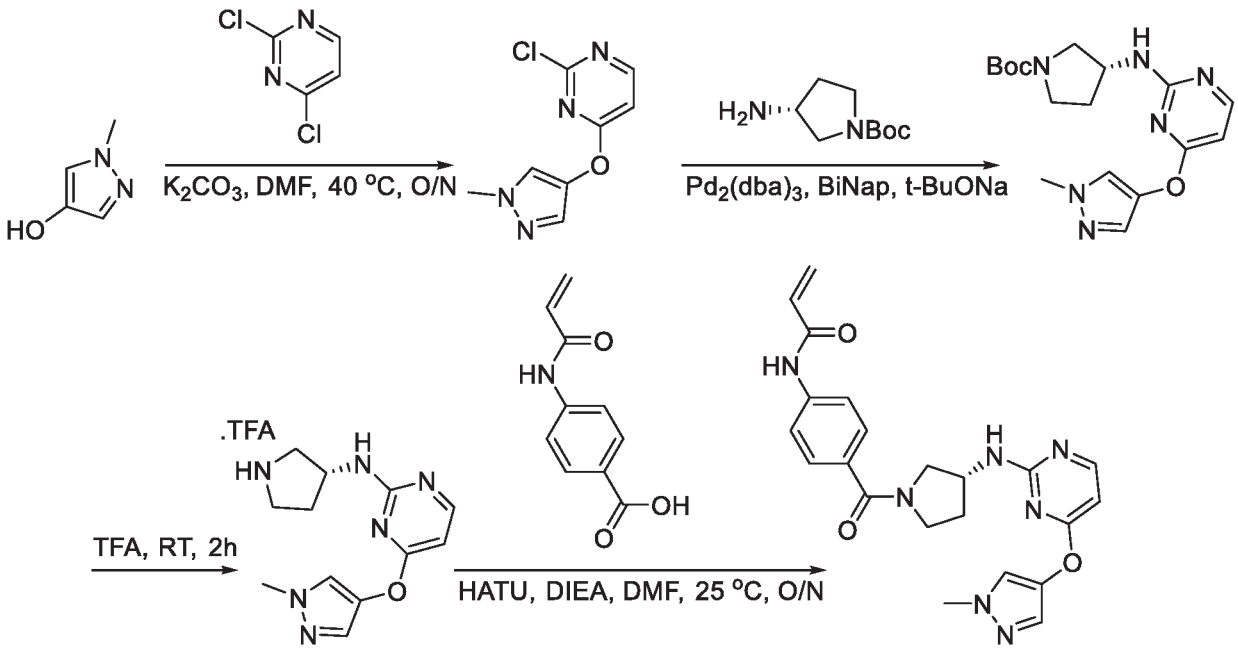
Step 2:

[00330] The title compound was prepared in 100% yield from 3-(4-cyclopentyloxy-pyrimidin-2-ylamino)-pyrrolidine-1-carboxylic acid tert-butyl ester using general procedure of (4-cyclopentyloxy-pyrimidin-2-yl)-piperidin-3-yl-amine. MS Calcd.: 248, MS Found: 249 ($[M+H]^+$).

Step 3:

[00331] The title compound was prepared in 27% yield from (4-cyclopentyloxy-pyrimidin-2-yl)-pyrrolidin-3-yl-amine using general procedure of N-{4-[3-(4-cyclopentyloxy-pyrimidin-2-ylamino)-piperidine-1-carbonyl]-phenyl}-acrylamide. ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.44-1.64 (m, 7H), 1.92-2.00 (m, 3H), 3.31-3.34 (m, 1H), 3.34-3.56 (m, 2H), 3.61-3.64 (m, 1H), 4.05-4.43 (m, 1H), 5.09-5.42 (m, 1H), 5.77-5.79 (m, 1H), 5.93-5.94 (m, 1H), 6.25-6.30 (m, 1H), 6.43-6.47 (m, 1H) 7.47-7.49 (m, 1H), 7.68-7.73 (m, 2H) 7.93-7.95 (m, 2H), 7.84-8.02 (m, 1H), 10.35 (s, 1H). MS Calcd.: 421, MS Found: 422 ($[M+H]^+$).

Example 46: Synthesis of N-(4-{3-[4-(1-Methyl-1H-pyrazol-4-yloxy)-pyrimidin-2-ylamino]-pyrrolidine-1-carbonyl}-phenyl)-acrylamide



Step 1:

[00332] To a solution of 1-methyl-1H-pyrazol-4-ol (1.0 g, 11.0 mmol) and 2,4-dichloropyrimidine (1.6 g, 11.0 mmol) in DMF (20 mL) was added K_2CO_3 (3.0 g, 22.0 mmol) at room temperature. The mixture was stirred at 40°C overnight. The mixture was water (100 mL) and extracted with DCM (50 mL*3). The combined organic layers were washed with water (100 mL*2) and brine (100 mL), dried over Na_2SO_4, filtered and concentrated *in vacuo* to give 2-chloro-4-((1-methyl-1H-pyrazol-4-yl)oxy)pyrimidine (2.2 g, 97%). MS Calcd.: 210, MS Found: 211 ([M+H]+).

Step 2:

[00333] To a solution of 2-chloro-4-((1-methyl-1H-pyrazol-4-yl)oxy)pyrimidine (800 mg, 3.8 mmol) and (R)-tert-butyl 3-aminopyrrolidine-1-carboxylate (1.1 g, 5.7 mmol) in toluene (20 mL) was added $Pd_2(dba)_3$ (696 mg, 0.8 mmol), BINAP (472 mg, 0.8 mmol) and t-BuONa (729 mg, 7.6 mmol) at room temperature under N_2. The mixture was stirred at 60°C for 5h under N_2. The mixture was then diluted with DCM (50 mL), washed with brine (50 mL), dried over Na_2SO_4, filtered and concentrated *in vacuo*. The residue was purified by flash chromatography on silica gel (Petroleum Ether/Ethyl Acetate = 1/1) to afford (R)-tert-butyl 3-((4-((1-methyl-1H-pyrazol-4-yl)oxy)pyrimidin-2-yl)amino)pyrrolidine-1-carboxylate (720 mg, 52%). MS Calcd.: 360, MS Found: 361 ($[M+H]^+$).

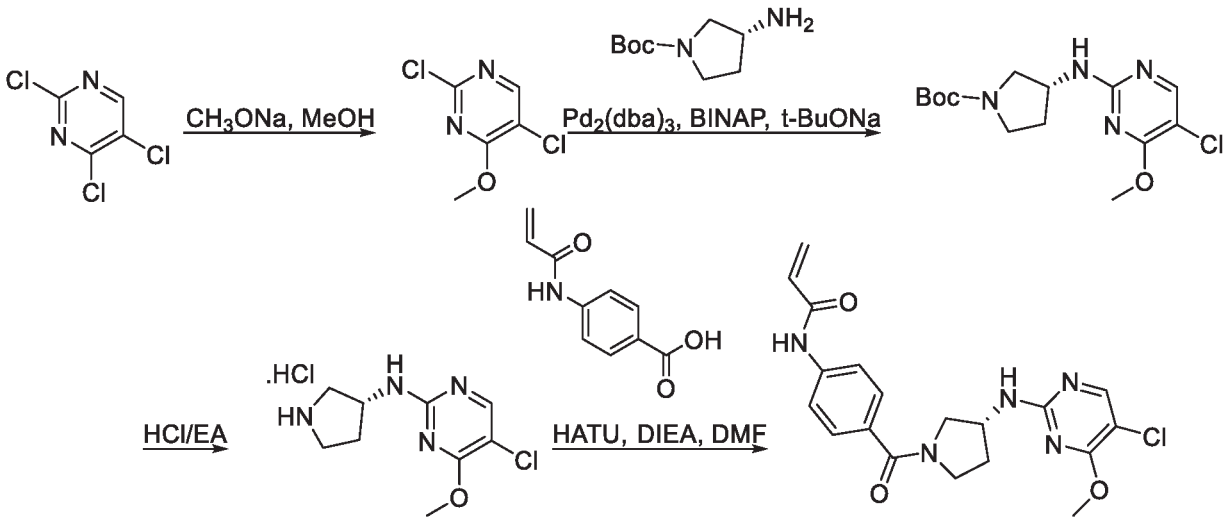
Step 3:

[00334] The title compound was prepared in 99% yield from 3-[4-(1-methyl-1H-pyrazol-4-yloxy)-pyrimidin-2-ylamino]-pyrrolidine-1-carboxylic acid tert-butyl ester using general procedure of (4-Cyclopentyloxy-pyrimidin-2-yl)-piperidin-3-yl-amine. MS Calcd.: 260, MS Found: 261 ($[M+H]^+$).

Step 4:

[00335] The title compound was prepared in 11% yield from (R)-4-((1-methyl-1H-pyrazol-4-yl)oxy)-N-(pyrrolidin-3-yl)pyrimidin-2-amine using general procedure of N-{4-[3-(4-Cyclopentyloxy-pyrimidin-2-ylamino)-piperidine-1-carbonyl]-phenyl}-acrylamide. ^1H NMR (400 MHz, CD_3OD): δ 2.01-2.29 (m, 2H), 3.46-3.90 (m, 7H), 4.33-4.51 (m, 1H), 5.81 (d, J = 9.6 Hz, 1H), 6.22 (d, J = 6.0 Hz, 0.6H), 6.28 (d, J = 6.0 Hz, 0.4H), 6.37-6.46 (m, 2H), 7.44-7.59 (m, 3H), 7.73-7.83 (m, 3H), 7.81 (d, J = 5.6 Hz, 0.6H), 8.16 (d, J = 5.6 Hz, 0.4H). MS Calcd.: 433, MS Found: 434($[M+H]^+$).

Example 47: Synthesis of (R)-N-(4-(3-((5-chloro-4-methoxypyrimidin-2-yl)amino)pyrrolidine-1-carbonyl)phenyl)acrylamide



Step 1:

[00336] To a solution of 2,4,5-trichloropyrimidine (2.0 g, 10.9 mmol) in MeOH (30 mL) was added sodium methoxide (590 mg, 10.9 mmol) at room temperature. The mixture was stirred at rt for 12h then concentrated *in vacuo*. The residue was purified by silica gel chromatography (Petroleum Ether/Ethyl Acetate = 20/1) to give 2,5-dichloro-4-methoxypyrimidine (1.0 g, 51%). MS Calcd.: 178, MS Found: 179 ($[M+H]^+$).

Step 2:

[00337] To a solution of 2,5-dichloro-4-methoxypyrimidine (400 mg, 2.27 mmol) in toluene (20 mL) was added (R)-tert-butyl 3-aminopyrrolidine-1-carboxylate (465 mg, 2.49 mmol), *t*-BuONa (326 mg, 3.40 mmol), $Pd_2(dba)_3$ (261 mg, 0.45 mmol) and BINAP (564 mg, 0.91 mmol) at RT under N_2. The mixture was stirred at 100°C for 12h and concentrated in-vacuo. The residue was purified by silica gel chromatography (Petroleum Ether/Ethyl Acetate = 1/1) to afford (R)-tert-butyl 3-((5-chloro-4-methoxypyrimidin-2-yl)amino)pyrrolidine-1-carboxylate (260 mg, 35%). MS Calcd.: 328, MS Found: 329 ($[M+H]^+$).

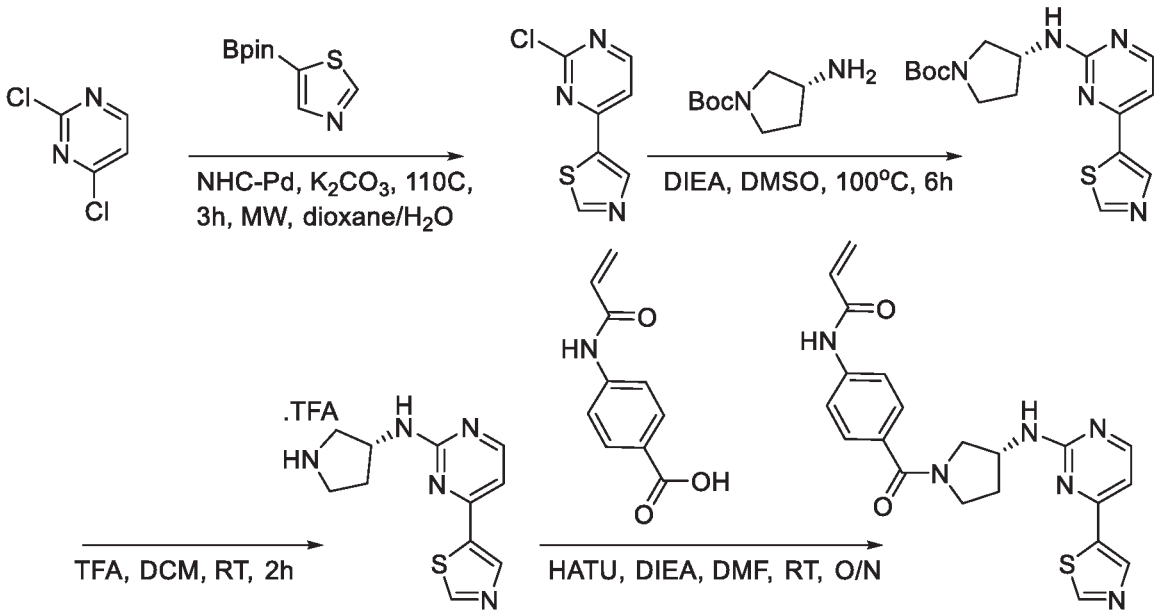
Step 3:

[00338] A solution of 3-((5-chloro-4-methoxypyrimidin-2-yl)amino)pyrrolidine-1-carboxylate (260 mg, 0.79 mmol) in HCl/Ethyl Acetate (10 mL, 2.0 M) was stirred at rt for 3h. The reaction mixture was then filtered to give (R)-5-chloro-4-methoxy-N-(pyrrolidin-3-yl)pyrimidin-2-amine hydrochloride (180 mg, 100%). MS Calcd.: 228, MS Found: 229 ($[M+H]^+$).

Step 4:

[00339] The title compound was prepared in 23% yield from (R)-5-chloro-4-methoxy-N-(pyrrolidin-3-yl)pyrimidin-2-amine hydrochloride using general procedure of N-{4-[3-(4-Cyclopentyloxy-pyrimidin-2-ylamino)-piperidine-1-carbonyl]-phenyl}-acrylamide. ^1H NMR (400 MHz, CD_3OD): δ 1.91-2.15 (m, 2H), 3.32-3.41 (m, 1H), 3.44-3.64 (m, 2H), 3.79 (m, 1H), 3.86-3.94 (m, 3H), 4.26 (m, 1H), 5.78 (d, J = 10.0 Hz, 1H), 6.28 (d, J = 14.8 Hz, 1H), 6.41-6.48 (m, 1H), 7.49-7.54 (m, 2H), 7.69-7.73 (m, 3H), 8.07-8.14 (m, 1H), 10.31 (s, 1H). MS Calcd.: 401, MS Found: 402 ($[M+H]^+$).

Example 48: Synthesis of N-{4-[3-(4-Thiazol-5-yl-pyrimidin-2-ylamino)-pyrrolidine-1-carbonyl]-phenyl}-acrylamide



Step 1:

[00340] To a solution of 5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)thiazole (200 mg, 0.95 mmol) and 2,4-dichloropyrimidine (95 mg, 0.63 mmol) in dioxane (5 mL) and H_2O (1 mL) was added NHC-Pd (20 mg, 0.06 mmol) and K_2CO_3 (174 mg, 1.26 mmol) at room temperature under N_2. The mixture was stirred at 110°C for 3h in microwave. The solution was diluted with DCM (50 mL) and washed with brine (20 mL). The organic layer was dried over Na_2SO_4, filtered and concentrated *in vacuo*. The residue was purified by *prep*-TLC (Petroleum Ether/Ethyl Acetate = 1/1) to give 5-(2-chloropyrimidin-4-yl)thiazole (40 mg, 35%). MS Calcd.: 197, MS Found: 198 ($[M+H]^+$).

Step 2:

[00341] To a solution of 5-(2-chloropyrimidin-4-yl)thiazole (40 mg, 0.2 mmol) and (R)-tert-butyl 3-aminopyrrolidine-1-carboxylate (57 mg, 0.3 mmol) in DMSO (5 mL) was added DIEA (52 mg, 0.4 mmol) at room temperature. The mixture was stirred at 100°C for then was diluted with water and filtered to give (R)-tert-butyl 3-((4-(thiazol-5-yl)pyrimidin-2-yl)amino)pyrrolidine-1-carboxylate (60 mg, 87%). MS Calcd.: 347, MS Found: 348 ($[M+H]^+$).

Step 3:

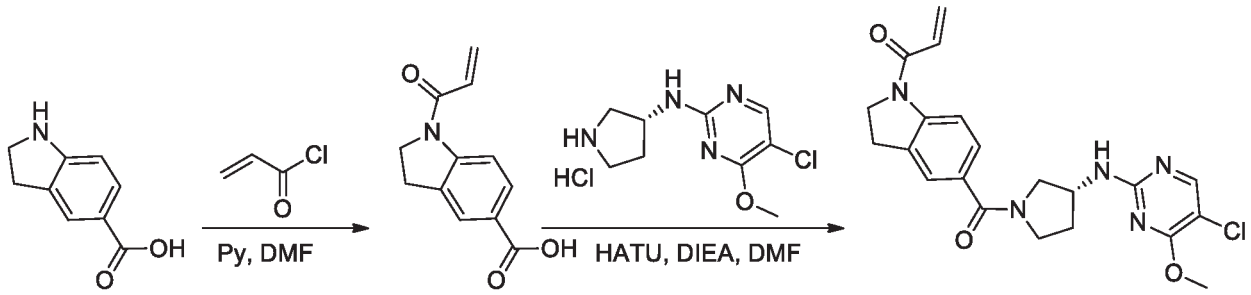
[00342] The title compound was prepared in 99% yield from(R)-tert-butyl 3-((4-(thiazol-5-yl)pyrimidin-2-yl)amino)pyrrolidine-1-carboxylate using general procedure of (4-Cyclopentyloxy-pyrimidin-2-yl)-piperidin-3-yl-amine. MS Calcd.: 247, MS Found: 248 ($[M+H]^+$).

Step 4:

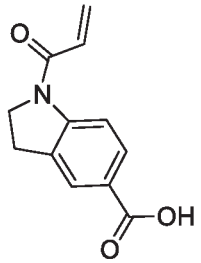
[00343] The title compound was prepared in 7% yield from (R)-N-(pyrrolidin-3-yl)-4-(thiazol-5-yl)pyrimidin-2-amine using general procedure of N-{4-[3-(4-Cyclopentyloxy-pyrimidin-2-ylamino)-piperidine-1-carbonyl]-phenyl}-acrylamide. ^1H NMR (400 MHz, CD_3OD): δ 1.89-2.11

(m, 1H), 2.12-2.29 (m, 1H), 3.39-3.71 (m, 3H), 3.89-3.90 (m, 1H), 4.30-4.52 (m, 1H), 5.67-5.71 (m, 1H), 6.28-6.34 (m, 2H), 7.00 (d, J = 5.2 Hz, 0.6H), 7.06 (d, J = 5.2 Hz, 0.4H), 7.42-7.49 (m, 2H), 7.61-7.67 (m, 2H), 8.17 (d, J = 5.6 Hz, 0.6H), 8.25 (d, J = 5.6 Hz, 0.4H), 8.41(s, 0.6H), 8.48 (s, 0.4H), 8.94 (s, 0.4H), 9.00 (s, 0.6H). MS Calcd.: 420, MS Found: 421([M+H]$^+$).

Example 49: Synthesis of (R)-1-(5-(3-((5-chloro-4-methoxypyrimidin-2-yl)amino)pyrrolidine-1-carbonyl)indolin-1-yl)prop-2-en-1-one

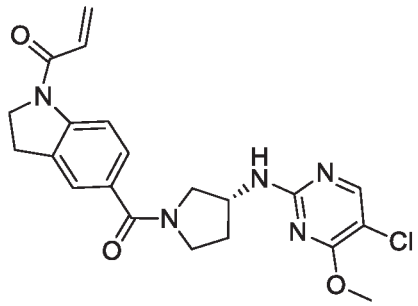


Step 1: 1-acryloylindoline-5-carboxylic acid



[00344] To a mixture of indoline-5-carboxylic acid (500 mg, 3.07 mmol) in DMF (3 mL) was added Pyridine (0.2 mL) at 0 °C followed by acryloyl chloride (555 mg, 6.13 mmol). The reaction mixture was stirred at RT for 5 h. The mixture was then concentrated, DCM was added (20 mL), washed with 0.5N HCl (10 mL), dried over Na_2SO_4, filted and concentrated *in vacuo* to afford 1-acryloylindoline-5-carboxylic acid (280 mg, 42%) as a yellow solid. [M+H] Calc'd for $C_{12}H_{11}NO_3$: 218.1; Found: 218.1

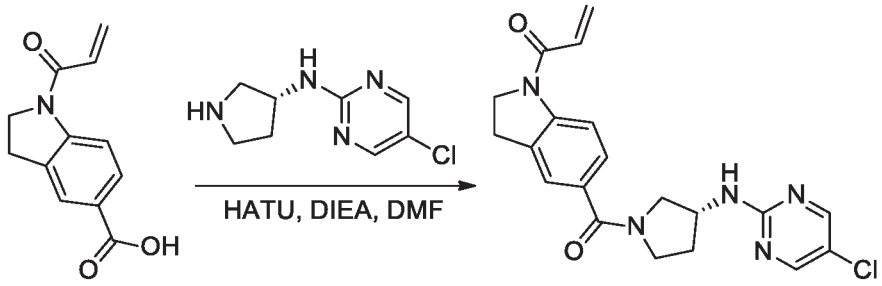
Step 2: (R)-1-(5-(3-((5-chloro-4-methoxypyrimidin-2-yl)amino)pyrrolidine-1-carbonyl)indolin-1-yl)prop-2-en-1-one



[00345] A mixture of 1-acryloylindoline-5-carboxylic acid (140 mg, 0.65 mmol), (R)-5-chloro-4-methoxy-N-(pyrrolidin-3-yl)pyrimidin-2-amine hydrochloride (221 mg, 0.84 mmol), HATU (368 mg, 0.97

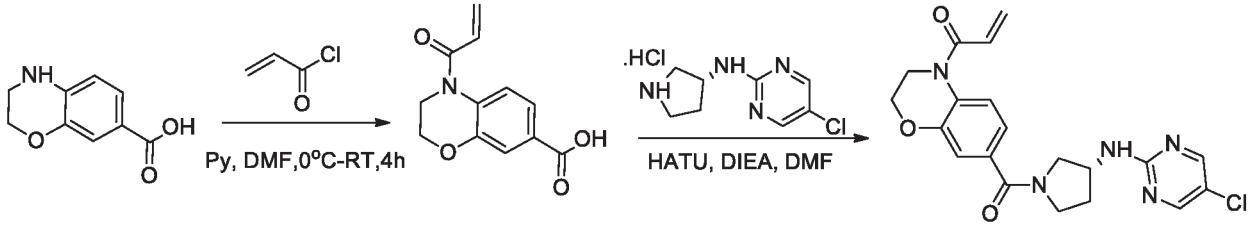
mmol) and DIEA (416 mg, 3.22 mmol) in DMF (5 mL) was stirred at RT overnight. The mixture was diluted with water (20 mL) and extracted with DCM (10 mL* 3). The combined organic layer was washed with brine (20 mL), dried over Na_2SO_4, filtered and concentrated in-vacuo. The residue was purified by *prep*-HPLC to afford (R)-1-(5-(3-((5-chloro-4-methoxypyrimidin-2-yl)amino)pyrrolidine-1-carbonyl)indolin-1-yl)prop-2-en-1-one (27 mg, 10%) as a yellow solid. ^{1}H NMR (400 MHz, CD_3OD): δ 2.00-2.10 (m, 1H), 2.21-2.35 (m, 1H), 3.22-3.27 (m, 2H), 3.46-3.96 (m, 6H), 4.00 (s, 1H), 4.25-4.29 (m, 2H), 4.37-4.55 (m, 1H), 5.86 (d, J = 10.4 Hz, 1H), 6.39-6.44 (m, 1H), 6.73-6.79 (m, 1H), 7.37-7.46 (m, 2H), 7.93 (s, 0.5H), 8.01(s, 0.5H) , 8.22 (br s, 1H). [M+H] Calc'd for $C_{21}H_{22}ClN_5O_3$: 428.2; Found: 428.2.

Example 50: Synthesis of (R)-1-(5-(3-((5-chloropyrimidin-2-yl)amino)pyrrolidine-1-carbonyl)indolin-1-yl)prop-2-en-1-one

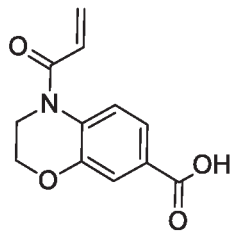


[00346] A mixture of 1-acryloylindoline-5-carboxylic acid (140 mg, 0.65 mmol), (R)-5-chloro-N-(pyrrolidin-3-yl)pyrimidin-2-amine (HCl salt) (196 mg, 0.84 mmol), HATU (368 mg, 0.97 mmol) and DIEA (416 mg, 3.22 mmol) in DMF (5 mL) was stirred at RT overnight. The mixture was diluted with water (20 mL) and extracted with DCM (10 mL* 3). The combined organic layer was washed with brine (20 mL), dried over Na_2SO_4, filtered and concentrated in-vacuo. The residue was purified by *prep*-HPLC to afford (R)-1-(5-(3-((5-chloropyrimidin-2-yl)amino)pyrrolidine-1-carbonyl)indolin-1-yl)prop-2-en-1-one (12 mg, 5%) as a white solid. ^{1}H NMR (400 MHz, CD_3OD): δ 1.99-2.10 (m, 1H), 2.21-2.35 (m, 1H), 3.22-3.29 (m, 2H), 3.44-3.95 (m, 4H), 4.25-4.31 (m, 2H), 4.36-4.55 (m, 1H), 5.86 (d, J = 10.4 Hz, 1H), 6.39-6.43 (m, 1H), 6.73-6.79 (m, 1H), 7.37-7.45 (m, 2H), 8.21 (s, 2H), 8.28(s, 1H). [M+H] Calc'd for $C_{20}H_{20}ClN_5O_2$, 398.1; Found, 398.1

Example 51: Synthesis of (R)-1-(7-(3-((5-chloropyrimidin-2-yl)amino)pyrrolidine-1-carbonyl)-2H-benzo[b][1,4]oxazin-4(3H)-yl)prop-2-en-1-one

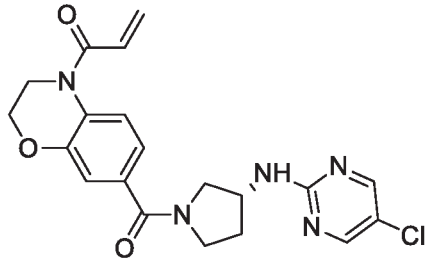


Step 1: 4-acryloyl-3,4-dihydro-2H-benzo[b][1,4]oxazine-7-carboxylic acid



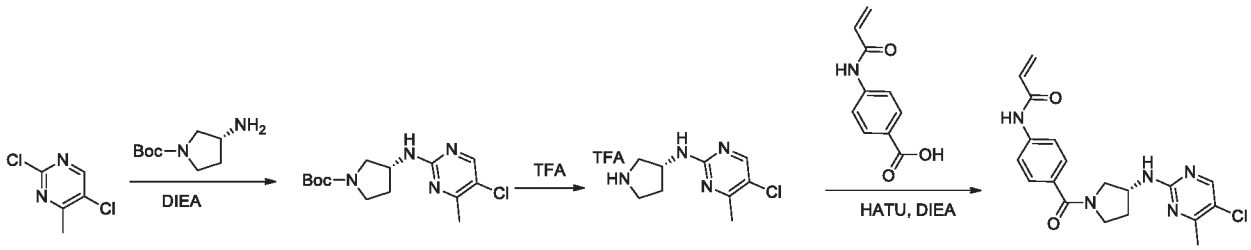
[00347] A mixture of 3,4-dihydro-2H-benzo[b][1,4]oxazine-7-carboxylic acid (800 mg, 4.47 mmol) in DMF (15 mL) was added Pyridine (1.0 mL) at 0°C, then added acryloyl chloride (603 mg, 6.66 mmol). The mixture was stirred at RT for 4 h. The mixture was concentrated and added DCM, washed with 1N HCl, dried over Na_2SO_4, filted, concentrated *in vacuo* to afford 4-acryloyl-3,4-dihydro-2H-benzo[b][1,4]oxazine-7-carboxylic acid (460 mg, 44%) as yellow solid. [M+H] Calc'd for $C_{12}H_{11}NO_4$: 234.1; Found: 234.1

Step 2: (R)-1-(7-(3-((5-chloropyrimidin-2-yl)amino)pyrrolidine-1-carbonyl)-2H-benzo[b][1,4]oxazin-4(3H)-yl)prop-2-en-1-one

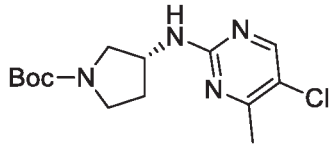


[00348] A mixture of 4-acryloyl-3,4-dihydro-2H-benzo[b][1,4]oxazine-7-carboxylic acid (200 mg, 0.86 mmol), (R)-5-chloro-N-(pyrrolidin-3-yl)pyrimidin-2-amine hydrochloride (200 mg, 0.86 mmol), HATU (653 mg, 1.72 mmol) and DIEA (553 mg, 4.29 mmol) in DMF (20 mL) was stirred at RT overnight. The mixture was diluted with water (20 mL) and extracted with DCM (20 mL* 3). The combined organic layer was washed with brine (20 mL), dried over Na_2SO_4, filtered and concentrated in-vacuo. The residue was purified by prep-HPLC to afford (R)-1-(7-(3-((5-chloropyrimidin-2-yl)amino)pyrrolidine-1-carbonyl)-2H-benzo[b][1,4]oxazin-4(3H)-yl)prop-2-en-1-one (34.6 mg, 8%) as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.86-2.13 (m, 2H), 3.34-3.77 (m, 4H),3.92-3.95 (m, 2H), 4.31-4.09 (m, 3H), 5.82-5.85 (m, 1H), 6.25-6.30 (m, 1H), 6.74-6.82 (m, 1H), 7.02-7.07 (m, 2H), 7.49 (br s, 1H), 7.81 (s, 1H), 8.32-8.38 (m, 2H). [M+H] Calc'd for $C_{20}H_{20}ClN_5O_3$, 414.1; Found, 414.1

Example 52: Synthesis of (R)-N-(4-(3-((5-chloro-4-methylpyrimidin-2-yl)amino)pyrrolidine-1-carbonyl)phenyl)acrylamide

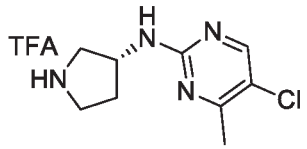


Step 1: (R)-tert-butyl 3-((5-chloro-4-methylpyrimidin-2-yl)amino)pyrrolidine-1-carboxylate



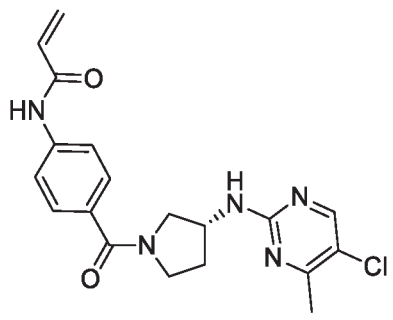
[00349] A mixture of 2,5-dichloro-4-methylpyrimidine (300 mg, 1.6 mmol), (R)-tert-butyl 3-aminopyrrolidine-1-carboxylate (263 mg, 1.6 mmol) and DIEA (619 mg, 4.8 mmol) in DMF (5 mL) was stirred at 120°C for 5 hours. The mixture was cooled to RT, diluted with water (20 mL) and extracted with EtOAc (20 mL* 3). The combined organic phase was washed with brine (20 mL), dried over Na_2SO_4, filtered and concentrated. The residue was purified by flash chromatography on silica gel (petroleum ether/EtOAc = 20/1) to afford (R)-tert-butyl 3-((5-chloro-4-methylpyrimidin-2-yl)amino)pyrrolidine-1-carboxylate (250 mg, 50%) as a yellow solid. [M+H] Calc'd for $C_{14}H_{21}ClN_4O_2$, 313.1; Found, 313.1.

Step 2: (R)-5-chloro-4-methyl-N-(pyrrolidin-3-yl)pyrimidin-2-amine 2,2,2-trifluoroacetate



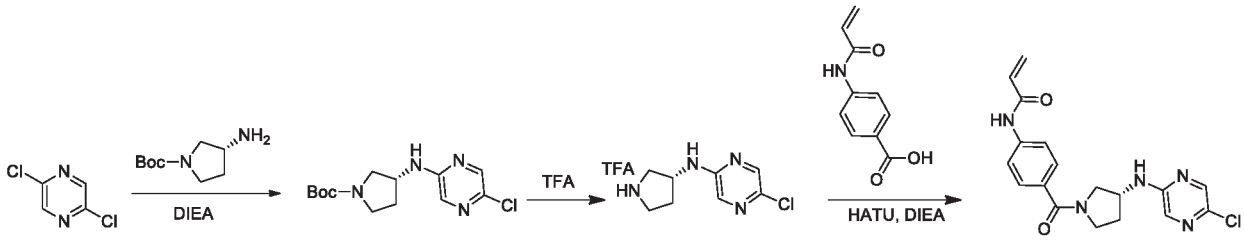
[00350] To a mixture of (R)-tert-butyl 3-((5-chloro-4-methylpyrimidin-2-yl)amino)pyrrolidine-1-carboxylate (120 mg, 0.38 mmol) in DCM (2 mL) was added TFA (1.5 mL). The mixture was stirred at RT for 15 minutes. The mixture was concentrated to afford (R)-5-chloro-4-methyl-N-(pyrrolidin-3-yl)pyrimidin-2-amine 2,2,2-trifluoroacetate (320 mg, crude, 100%) as yellow oil. [M+H] Calc'd for $C_9H_{13}ClN_4$, 213.6; Found, 213.6.

Step 3: (R)-N-(4-(3-((5-chloro-4-methylpyrimidin-2-yl)amino)pyrrolidine-1-carbonyl)phenyl)acrylamide

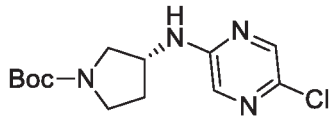


[00351] A mixture of (R)-5-chloro-4-methyl-N-(pyrrolidin-3-yl)pyrimidin-2-amine 2,2,2-trifluoroacetate (300 mg, crude, 0.38 mmol), 4-acrylamidobenzoic acid (73 mg, 0.38 mmol), HATU (174 mg, 0.46 mmol) and DIEA (147 mg, 1.14 mmol) in DMF (2 mL) was stirred at RT overnight. The mixture was diluted with water (20 mL) and extracted with EtOAc (20 mL* 3). The combined organic phase was washed with brine (20 mL), dried over Na_2SO_4, filtered and concentrated. The residue was purified by *prep*-HPLC to afford (R)-N-(4-(3-((5-chloro-4-methylpyrimidin-2-yl)amino)pyrrolidine-1-carbonyl)phenyl)acrylamide (40 mg, 27%) as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.95-2.00 (m, 1H), 2.24-2.42 (m, 4H), 3.35-3.88 (m, 4H), 4.47-4.58 (m, 1H), 5.13-5.29 (m, 1H), 5.78 (d, J = 11.2 Hz, 1H), 6.25-6.32 (m, 1H), 6.42-6.47 (m, 1H), 7.45-7.48 (m, 2H), 7.56 (m, 2H), 7.88 (s, 1H), 8.08 (s, 0.5H), 8.14 (s, 0.5H). [M+H] Calc'd for $C_{19}H_{20}ClN_5O_2$, 386.1; Found, 386.1.

Example 53: Synthesis of (R)-N-(4-(3-((5-chloropyrazin-2-yl)amino)pyrrolidine-1-carbonyl)phenyl)acrylamide

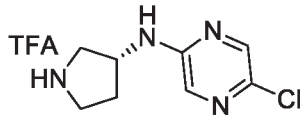


Step 1: (R)-tert-butyl 3-((5-chloropyrazin-2-yl)amino)pyrrolidine-1-carboxylate



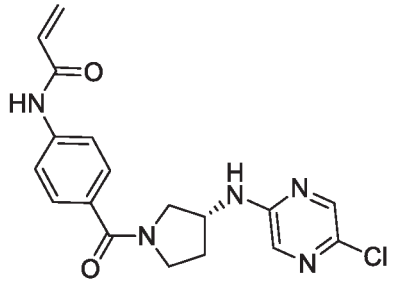
[00352] The title compound was prepared in 16% yield from 2,5-dichloropyrazine using general procedure of (R)-tert-butyl 3-((5-chloro-4-methylpyrimidin-2-yl)amino)pyrrolidine-1-carboxylate. [M+H] Calc'd for $C_{13}H_{19}ClN_4O_2$, 299.1; Found, 299.1.

Step 2: (R)-5-chloro-N-(pyrrolidin-3-yl)pyrazin-2-amine 2,2,2-trifluoroacetate



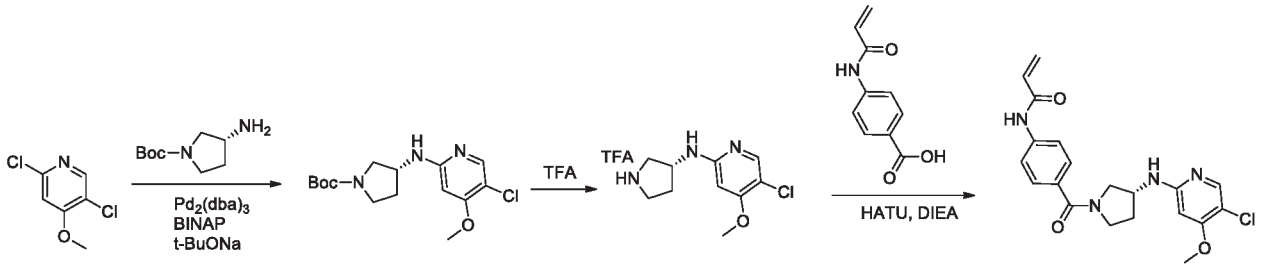
[00353] The title compound was prepared in 100% yield from (R)-tert-butyl 3-((5-chloropyrazin-2-yl)amino)pyrrolidine-1-carboxylate using general procedure of (R)-5-chloro-4-methyl-N-(pyrrolidin-3-yl)pyrimidin-2-amine 2,2,2-trifluoroacetate. [M+H] Calc'd for $C_8H_{11}ClN_4$, 199.0; Found, 199.0.

Step 3: (R)-N-(4-(3-((5-chloropyrazin-2-yl)amino)pyrrolidine-1-carbonyl)phenyl)acrylamide

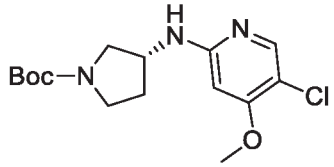


[00354] The title compound was prepared in 28% yield from (R)-5-chloro-N-(pyrrolidin-3-yl)pyrazin-2-amine 2,2,2-trifluoroacetate using general procedure of (R)-N-(4-(3-((5-chloro-4-methylpyrimidin-2-yl)amino)pyrrolidine-1-carbonyl)phenyl)acrylamide. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.99-2.00 (m, 1H), 2.21-2.37 (m, 1H), 3.60-3.84 (m, 4H), 4.40-4.41 (m, 1H), 5.27-5.44 (m, 1H), 5.78 (d, J = 11.2 Hz, 1H), 6.26-6.33 (m, 1H), 6.42-6.46 (m, 1H), 7.40-7.42 (m, 2H), 7.53-7.55 (m, 2H), 7.66 (s, 0.5H), 7.75 (s, 0.5H), 7.95-8.10 (m, 2H). [M+H] Calc'd for $C_{18}H_{18}ClN_5O_2$, 372.1; Found, 372.1.

Example 54: Synthesis of (R)-N-(4-(3-((5-chloro-4-methoxypyridin-2-yl)amino)pyrrolidine-1-carbonyl)phenyl)acrylamide

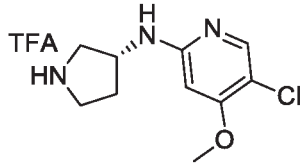


Step 1: (R)-tert-butyl 3-((5-chloro-4-methoxypyridin-2-yl)amino)pyrrolidine-1-carboxylate



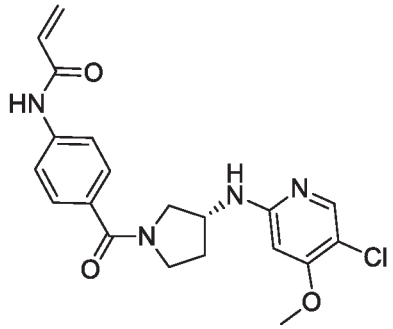
[00355] The title compound was prepared in 53% yield from 2,5-dichloro-4-methoxypyridine using general procedure of (R)-tert-butyl 3-((5-chloro-4-methylpyrimidin-2-yl)amino)pyrrolidine-1-carboxylate. [M+H] Calc'd for $C_{15}H_{22}ClN_3O_3$, 328.1; Found, 328.1.

Step 2: (R)-5-chloro-4-methoxy-N-(pyrrolidin-3-yl)pyridin-2-amine 2,2,2-trifluoroacetate



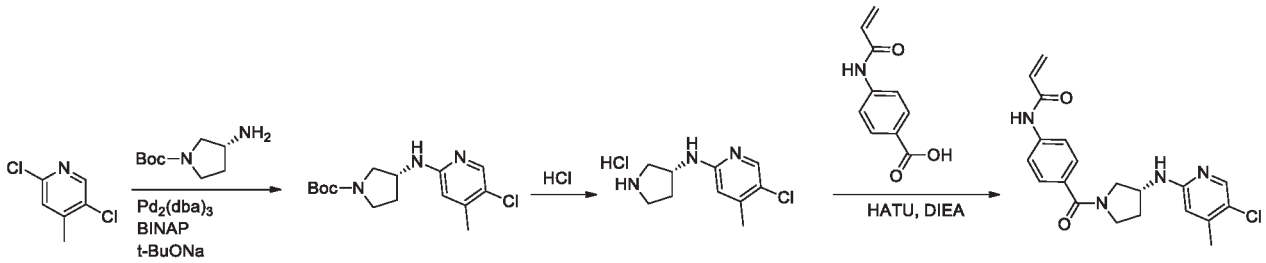
[00356] The title compound was prepared in 100% yield from (R)-tert-butyl 3-((5-chloro-4-methoxypyridin-2-yl)amino)pyrrolidine-1-carboxylate using general procedure of (R)-5-chloro-4-methyl-N-(pyrrolidin-3-yl)pyrimidin-2-amine 2,2,2-trifluoroacetate. [M+H] Calc'd for $C_{10}H_{14}ClN_3O$, 228.0; Found, 228.0.

Step 3: (R)-N-(4-(3-((5-chloro-4-methoxypyridin-2-yl)amino)pyrrolidine-1-carbonyl)phenyl)acrylamide

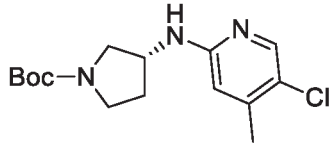


[00357] The title compound was prepared in 14% yield from (R)-5-chloro-4-methoxy-N-(pyrrolidin-3-yl)pyridin-2-amine 2,2,2-trifluoroacetate using general procedure of (R)-N-(4-(3-((5-chloro-4-methylpyrimidin-2-yl)amino)pyrrolidine-1-carbonyl)phenyl)acrylamide. ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.80-1.90 (m, 1H), 2.07-2.20 (m, 1H), 3.35-3.39 (m, 1H), 3.51-3.63 (m, 2H), 3.68-3.82 (m, 4H), 4.25-4.41 (m, 1H), 5.78 (d, J = 10.0 Hz, 1H), 6.14-6.18 (m, 1H), 6.26-6.30 (m, 1H), 6.40-6.47 (m, 1H), 6.92-6.99 (m, 1H), 7.49-7.54 (m, 2H), 7.69-7.77 (m, 2H), 7.78 (s, 0.5H), 7.88 (s, 0.5H), 10.30 (s, 1H). [M+H] Calc'd for $C_{20}H_{21}ClN_4O_3$, 401.1; Found, 401.1.

Example 55: Synthesis of (R)-N-(4-(3-((5-chloro-4-methylpyridin-2-yl)amino)pyrrolidine-1-carbonyl)phenyl)acrylamide

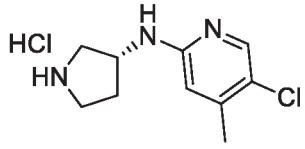


Step 1: (R)-tert-butyl 3-((5-chloro-4-methylpyridin-2-yl)amino)pyrrolidine-1-carboxylate



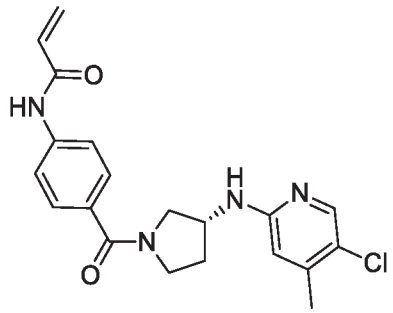
[00358] The title compound was prepared in 87% yield from 2,5-dichloro-4-methylpyridine using general procedure of (R)-tert-butyl 3-((5-chloro-4-methylpyrimidin-2-yl)amino)pyrrolidine-1-carboxylate. [M+H] Calc'd for $C_{15}H_{22}ClN_3O_2$, 312.1; Found, 312.1.

Step 2: (R)-5-chloro-4-methyl-N-(pyrrolidin-3-yl)pyridin-2-amine hydrochloride



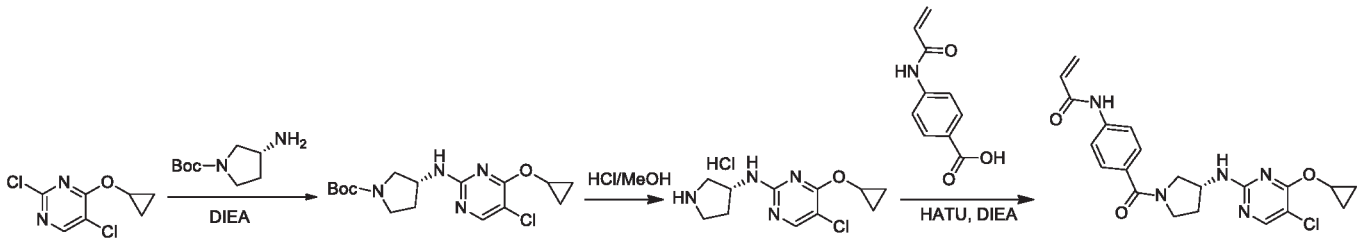
[00359] A mixture of (R)-tert-butyl 3-((5-chloro-4-methylpyridin-2-yl)amino)pyrrolidine-1-carboxylate (500 mg, 1.64 mmol) in HCl/EtOAc (4M, 10 mL) was stirred at 15 °C for 30 minutes. The mixture was concentrated to afford (R)-5-chloro-4-methyl-N-(pyrrolidin-3-yl)pyridin-2-amine hydrochloride (480 mg, crude, 100%) as a yellow solid. [M+H] Calc'd for $C_{10}H_{14}ClN_3$, 212.0; Found, 212.0.

Step 3: (R)-N-(4-(3-((5-chloro-4-methylpyridin-2-yl)amino)pyrrolidine-1-carbonyl)phenyl)acrylamide

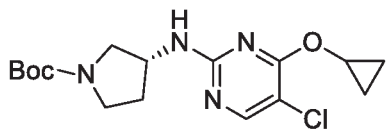


[00360] The title compound was prepared in 8% yield from (R)-5-chloro-4-methyl-N-(pyrrolidin-3-yl)pyridin-2-amine hydrochloride using general procedure of (R)-N-(4-(3-((5-chloro-4-methylpyrimidin-2-yl)amino)pyrrolidine-1-carbonyl)phenyl)acrylamide. ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.81-1.91 (m, 1H), 2.15-2.20 (m, 4H), 3.26-3.32 (m, 1H), 3.50-3.64 (m, 2H), 3.77-3.79 (m, 1H), 4.21-4.35 (m, 1H), 5.78 (d, J = 9.6 Hz, 1H), 6.26-6.30 (m, 1H), 6.40-6.48 (m, 2H), 6.91-6.96 (m, 1H), 7.49-7.54 (m, 2H), 7.69-7.74 (m, 2H), 7.86 (s, 0.6H), 7.96 (s, 0.4H), 10.33 (br s, 1H). [M+H] Calc'd for $C_{20}H_{21}ClN_4O_2$, 385.1; Found, 385.1.

Example 56: Synthesis of (*R*)-*N*-(4-(3-((5-chloro-4-cyclopropoxypyrimidin-2-yl)amino)pyrrolidine-1-carbonyl)phenyl)acrylamide

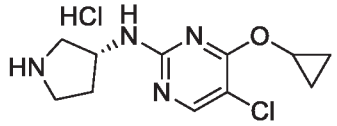


Step 1: (R)-tert-butyl 3-((5-chloro-4-cyclopropoxypyrimidin-2-yl)amino)pyrrolidine-1-carboxylate



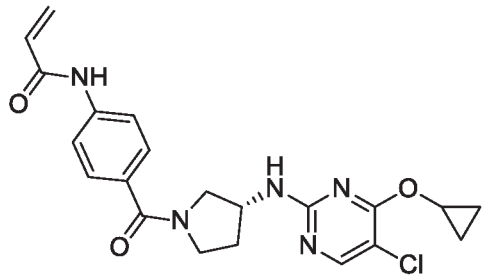
[00361] The title compound was prepared in 42% yield from 2,5-dichloro-4-cyclopropoxypyrimidine using general procedure of (R)-tert-butyl 3-((5-chloro-4-methylpyrimidin-2-yl)amino)pyrrolidine-1-carboxylate. [M+H] Calc'd for $C_{16}H_{23}ClN_4O_3$, 355.1; Found, 355.1.

Step 2: (R)-5-chloro-4-cyclopropoxy-N-(pyrrolidin-3-yl)pyrimidin-2-amine hydrochloride



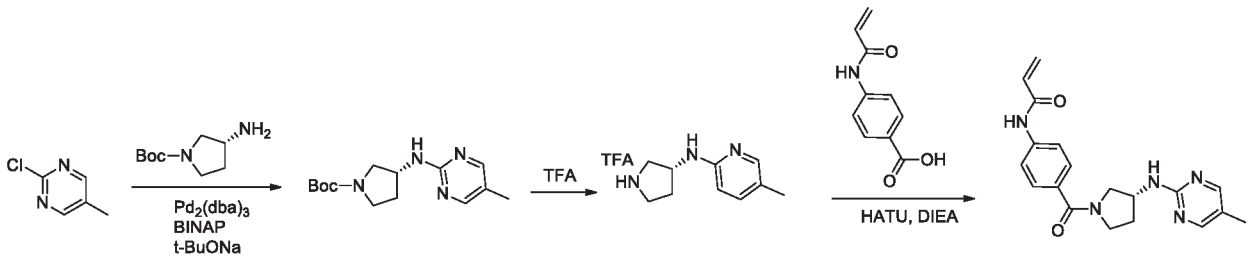
[00362] A mixture of (R)-tert-butyl 3-((5-chloro-4-cyclopropoxypyrimidin-2-yl)amino)pyrrolidine-1-carboxylate (800 mg, 2.26 mmol) in MeOH (4 mL) was added HCl/MeOH (2M, 2 mL). The mixture was stirred at 35°C for 3 hours. The mixture was concentrated to afford (R)-5-chloro-4-cyclopropoxy-N-(pyrrolidin-3-yl)pyrimidin-2-amine hydrochloride (574 mg, crude, 100%) as a white solid. [M+H] Calc'd for $C_{11}H_{15}ClN_4O$, 255.0; Found, 255.0.

Step 3: (R)-N-(4-(3-((5-chloro-4-cyclopropoxypyrimidin-2-yl)amino)pyrrolidine-1-carbonyl)phenyl)acrylamide

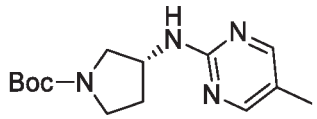


[00363] The title compound was prepared in 23% yield from (R)-5-chloro-4-cyclopropoxy-N-(pyrrolidin-3-yl)pyrimidin-2-amine hydrochloride using general procedure of (R)-N-(4-(3-((5-chloro-4-methylpyrimidin-2-yl)amino)pyrrolidine-1-carbonyl)phenyl)acrylamide. ^{1}H NMR (400 MHz, DMSO-d_6): δ 0.61-0.80 (m, 4H), 1.90-2.04 (m, 1H), 2.07-2.15 (m, 1H), 3.38-3.47 (m, 1H), 3.51-3.57 (m, 1H), 3.63-3.65 (m, 1H), 3.77-3.80 (m, 1H), 4.20-4.25 (m, 1H), 4.34-4.41 (m, 1H), 5.77-5.80 (m, 1H), 6.25-6.30 (m, 1H), 6.41-6.47 (m, 1H), 7.48-7.53 (m, 2H), 7.68-7.73 (m, 3H), 8.07-8.14 (m, 1H), 10.29 (s, 1H). [M+H] Calc'd for $C_{21}H_{22}ClN_5O_3$, 428.1; Found, 428.1.

<u>Example 57: Synthesis of (R)-N-(4-(3-((5-methylpyrimidin-2-yl)amino)pyrrolidine-1-carbonyl)phenyl)acrylamide</u>

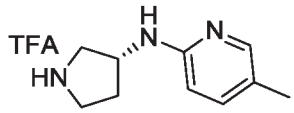


Step 1: (R)-tert-butyl 3-((5-methylpyrimidin-2-yl)amino)pyrrolidine-1-carboxylate



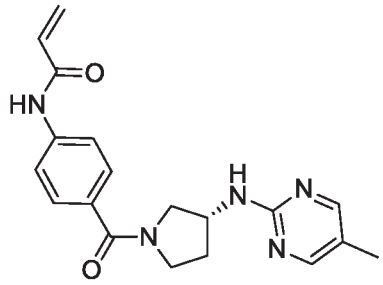
[00364] The title compound was prepared in 32% yield from 2-chloro-5-methylpyrimidine using general procedure of (R)-tert-butyl 3-((5-chloro-4-methylpyrimidin-2-yl)amino)pyrrolidine-1-carboxylate. [M+H] Calc'd for $C_{14}H_{22}N_4O_2$, 279.1; Found, 279.1.

Step 2: (R)-5-methyl-N-(pyrrolidin-3-yl)pyridin-2-amine 2,2,2-trifluoroacetate



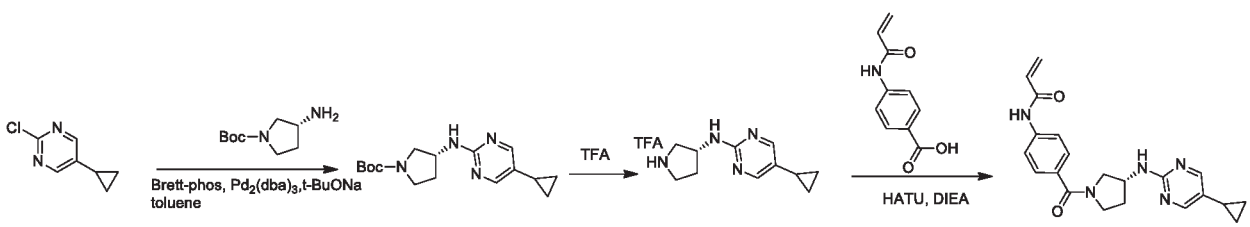
[00365] The title compound was prepared in 100% yield from (R)-tert-butyl 3-((5-methylpyrimidin-2-yl)amino)pyrrolidine-1-carboxylate using general procedure of (R)-5-chloro-4-methyl-N-(pyrrolidin-3-yl)pyrimidin-2-amine 2,2,2-trifluoroacetate. [M+H] Calc'd for $C_{10}H_{15}N_3$, 178.1; Found, 178.1.

Step 3: (R)-N-(4-(3-((5-methylpyrimidin-2-yl)amino)pyrrolidine-1-carbonyl)phenyl)acrylamide

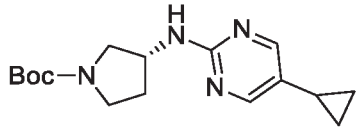


[00366] The title compound was prepared in 34% yield from (R)-5-methyl-N-(pyrrolidin-3-yl)pyridin-2-amine 2,2,2-trifluoroacetate using general procedure of (R)-N-(4-(3-((5-chloro-4-methylpyrimidin-2-yl)amino)pyrrolidine-1-carbonyl)phenyl)acrylamide. ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.82-2.19 (m, 5H), 3.35-3.42 (m, 1H), 3.47-3.55 (m, 1H), 3.62-3.69 (m, 1H), 3.73-3.78 (m, 1H), 4.22-4.44 (m, 1H), 5.78 (d, J = 10.4 Hz, 1H), 6.26-6.30 (m, 1H), 6.40-6.47 (m, 1H), 7.22-7.25 (m, 1H), 7.47-7.53 (m, 2H), 7.67-7.73 (m, 2H), 8.09 (s, 1H), 8.17 (s, 1H), 10.29 (s, 1H). [M+H] Calc'd for $C_{19}H_{21}N_5O_2$, 352.1; Found, 352.1.

<u>Example 58: Synthesis of (R)-N-(4-(3-((5-cyclopropylpyrimidin-2-yl)amino)pyrrolidine-1-carbonyl)phenyl)acrylamide</u>

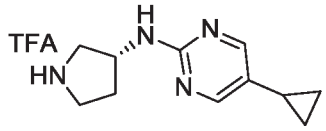


Step 1: (R)-tert-butyl 3-((5-cyclopropylpyrimidin-2-yl)amino)pyrrolidine-1-carboxylate



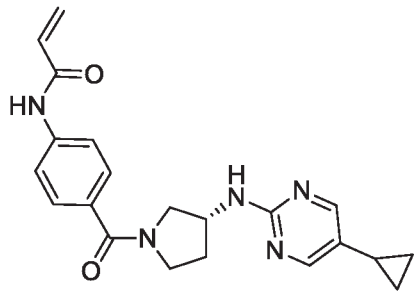
[00367] A mixture of 2-chloro-5-cyclopropylpyrimidine (200 mg, 1.3 mmol), (R)-tert-butyl 3-aminopyrrolidine-1-carboxylate (242 mg, 1.3 mmol), Brett-phos (107 mg, 0.2 mmol), $Pd_2(dba)_3$ (59 mg, 0.07 mmol) and t-BuONa (250 mg, 2.6 mmol) in toluene (5 mL) was stirred at 100°C under N_2 overnight. The mixture was cooled to RT and concentrated. The residue was purified by flash chromatography on silica gel (petroleum ether/EtOAc = 50/1 to petroleum ether /EtOAc = 1/1) to afford (R)-tert-butyl 3-((5-cyclopropylpyrimidin-2-yl)amino)pyrrolidine-1-carboxylate (50 mg, 11%) as yellow oil. [M+H] Calc'd for $C_{16}H_{24}N_4O_2$, 305.1; Found, 305.1.

Step 2: (R)-5-cyclopropyl-N-(pyrrolidin-3-yl)pyrimidin-2-amine 2,2,2-trifluoroacetate



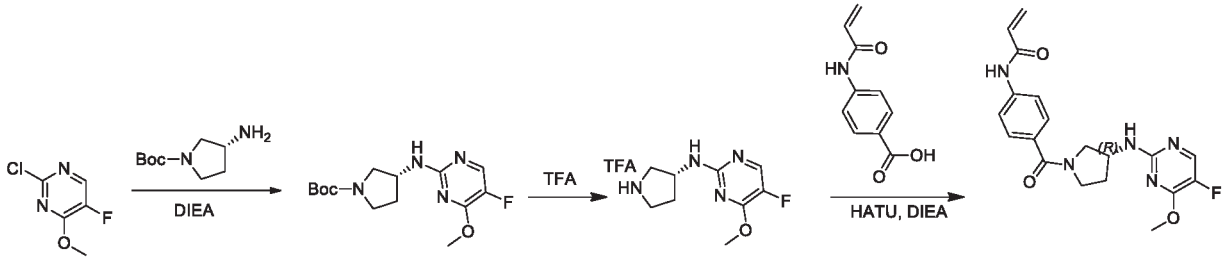
[00368] The title compound was prepared in 100% yield from (R)-tert-butyl 3-((5-cyclopropylpyrimidin-2-yl)amino)pyrrolidine-1-carboxylate using general procedure of (R)-5-chloro-4-methyl-N-(pyrrolidin-3-yl)pyrimidin-2-amine 2,2,2-trifluoroacetate. [M+H] Calc'd for $C_{11}H_{16}N_4$, 205.1; Found, 205.1.

Step 3: (R)-N-(4-(3-((5-cyclopropylpyrimidin-2-yl)amino)pyrrolidine-1-carbonyl)phenyl)acrylamide

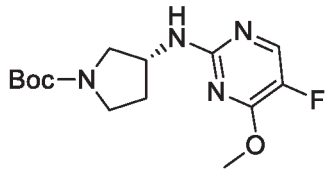


[00369] The title compound was prepared in 29% yield from (R)-5-cyclopropyl-N-(pyrrolidin-3-yl)pyrimidin-2-amine 2,2,2-trifluoroacetate using general procedure of (R)-N-(4-(3-((5-chloro-4-methylpyrimidin-2-yl)amino)pyrrolidine-1-carbonyl)phenyl)acrylamide. ^{1}H NMR (400 MHz, DMSO-d_6): δ 0.57-0.62 (m, 2H), 0.81-0.86 (m, 2H), 1.68-2.17 (m, 3H), 3.37-3.79 (m, 4H), 4.22-4.24 (m, 0.5H), 4.39-4.41 (m, 0.5H), 5.78 (d, J = 10.8 Hz, 1H), 6.25-6.30 (m, 1H), 6.40-6.47 (m, 1H), 7.28 (s, 1H), 7.48-7.53 (m, 2H), 7.68-7.73 (m, 2H), 8.05 (s, 1H), 8.12 (s, 1H), 10.31 (s, 1H). [M+H] Calc'd for $C_{21}H_{23}N_5O_2$, 378.1; Found, 378.1.

Example 59: Synthesis of (R)-N-(4-(3-((5-fluoro-4-methoxypyrimidin-2-yl)amino)pyrrolidine-1-carbonyl)phenyl)acrylamide

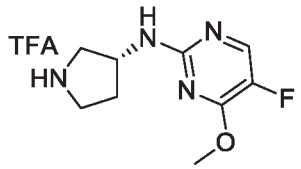


Step 1: (R)-tert-butyl 3-((5-fluoro-4-methoxypyrimidin-2-yl)amino)pyrrolidine-1-carboxylate



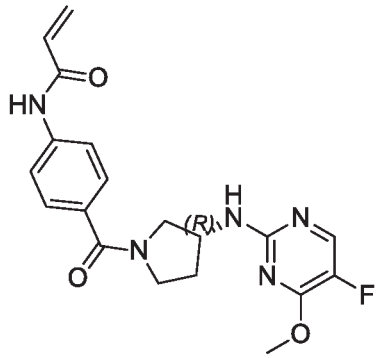
[00370] The title compound was prepared in 32% yield from 2-chloro-5-fluoro-4-methoxypyrimidine using general procedure of (R)-tert-butyl 3-((5-chloro-4-methylpyrimidin-2-yl)amino)pyrrolidine-1-carboxylate. [M+H] Calc'd for $C_{14}H_{21}FN_4O_3$, 313.1; Found, 313.1.

Step 2: (R)-5-fluoro-4-methoxy-N-(pyrrolidin-3-yl)pyrimidin-2-amine 2,2,2-trifluoroacetate



[00371] The title compound was prepared in 90% yield from (R)-tert-butyl 3-((5-fluoro-4-methoxypyrimidin-2-yl)amino)pyrrolidine-1-carboxylate using general procedure of (R)-5-chloro-4-methyl-N-(pyrrolidin-3-yl)pyrimidin-2-amine 2,2,2-trifluoroacetate. [M+H] Calc'd for $C_9H_{13}FN_4O$, 213.1; Found, 213.1.

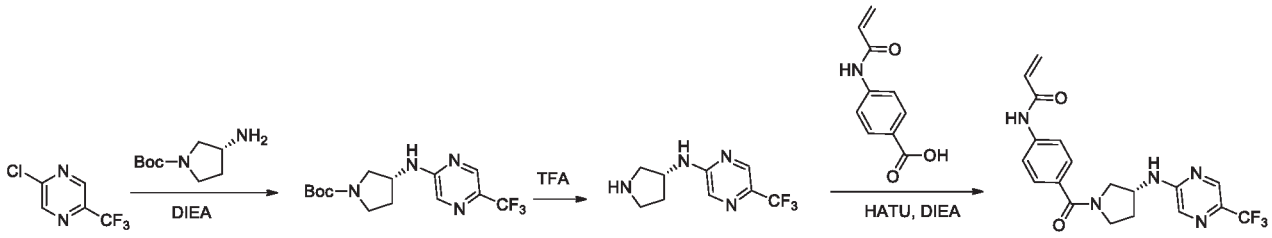
Step 3: (R)-N-(4-(3-((5-fluoro-4-methoxypyrimidin-2-yl)amino)pyrrolidine-1-carbonyl)phenyl)acrylamide



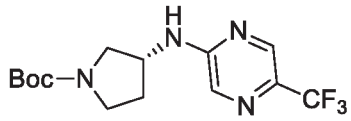
[00372] The title compound was prepared in 7.5% yield from (R)-5-fluoro-4-methoxy-N-(pyrrolidin-3-yl)pyrimidin-2-amine 2,2,2-trifluoroacetate using general procedure of (R)-N-(4-(3-((5-chloro-4-

methylpyrimidin-2-yl)amino)pyrrolidine-1-carbonyl)phenyl)acrylamide. ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.86-2.00 (m, 1H), 2.07-2.17 (m, 1H), 3.35-3.44 (m, 1H), 3.47-3.56 (m, 1H), 3.60-3.79 (m, 2H), 3.86 (s, 1.5H), 3.94 (s, 1.5H), 4.20-4.22 (m, 0.5H), 4.37-4.39 (m, 0.5H), 5.78 (d, J = 12.0 Hz, 1H), 6.27 (d, J = 16.8 Hz, 1H), 6.41-6.47 (m, 1H), 7.41-7.45 (m, 1H), 7.48-7.53 (m, 2H), 7.68-7.73 (m, 2H), 8.05 (d, J = 2.8 Hz, 0.5H), 8.12 (d, J = 2.8 Hz, 0.5H), 10.30 (s, 1H). [M+H] Calc'd for $C_{19}H_{20}FN_5O_3$, 386.1; Found, 386.1.

Example 60: Synthesis of (R)-N-(4-(3-((5-(trifluoromethyl)pyrazin-2-yl)amino)pyrrolidine-1-carbonyl)phenyl)acrylamide

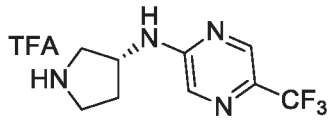


Step 1: (R)-tert-butyl 3-((5-(trifluoromethyl)pyrazin-2-yl)amino)pyrrolidine-1-carboxylate



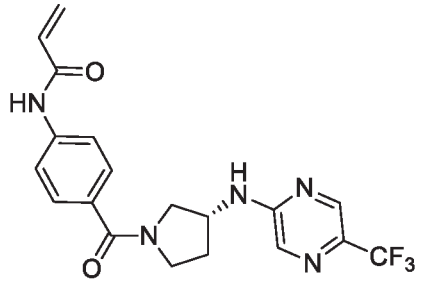
[00373] The title compound was prepared in 43% yield from 2-chloro-5-(trifluoromethyl)pyrazine using general procedure of (R)-tert-butyl 3-((5-chloro-4-methylpyrimidin-2-yl)amino)pyrrolidine-1-carboxylate. [M+H] Calc'd for $C_{14}H_{19}F_3N_4O_2$, 333.1; Found, 333.1.

Step 2: (R)-N-(pyrrolidin-3-yl)-5-(trifluoromethyl)pyrazin-2-amine 2,2,2-trifluoroacetate



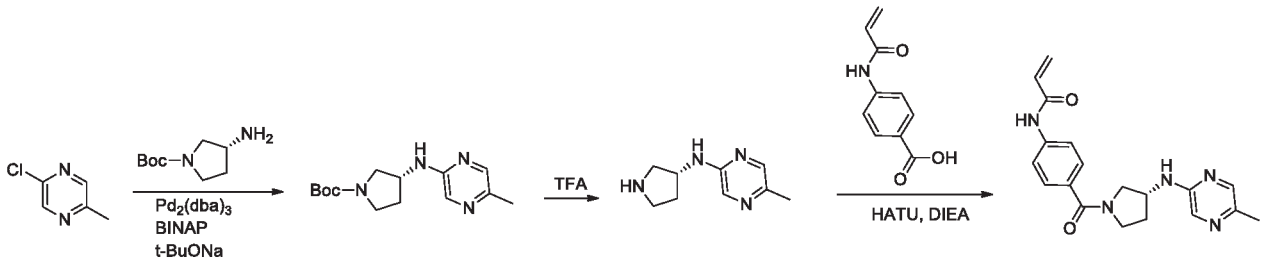
[00374] The title compound was prepared in 100% yield from (R)-tert-butyl 3-((5-(trifluoromethyl)pyrazin-2-yl)amino)pyrrolidine-1-carboxylate using general procedure of (R)-5-chloro-4-methyl-N-(pyrrolidin-3-yl)pyrimidin-2-amine 2,2,2-trifluoroacetate. [M+H] Calc'd for $C_9H_{11}F_3N_4$, 233.0; Found, 233.0.

Step 3: (R)-N-(4-(3-((5-(trifluoromethyl)pyrazin-2-yl)amino)pyrrolidine-1-carbonyl)phenyl)acrylamide

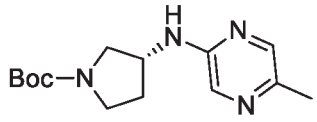


[00375] The title compound was prepared in 26% yield from (R)-N-(pyrrolidin-3-yl)-5-(trifluoromethyl)pyrazin-2-amine 2,2,2-trifluoroacetate using general procedure of (R)-N-(4-(3-((5-chloro-4-methylpyrimidin-2-yl)amino)pyrrolidine-1-carbonyl)phenyl)acrylamide. ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.91-1.98 (m, 1H), 2.19-2.22 (m, 1H), 3.37-3.48 (m, 1H), 3.56-3.65 (m, 2H), 3.80-3.86 (m, 1H), 4.37-4.47 (m, 1H), 5.78 (d, J = 10.8 Hz, 1H), 6.28 (d, J = 16.8 Hz, 1H), 6.41-6.47 (m, 1H), 7.50-7.54 (m, 2H), 7.69-7.74 (m, 2H), 8.00 (s, 0.5H), 8.04 (s, 0.5H), 8.18-8.26 (m, 1H), 8.35 (s, 0.5H), 8.44 (s, 0.5H), 10.30 (s, 1H). [M+H] Calc'd for $C_{19}H_{18}F_3N_5O_2$, 406.1; Found, 406.1.

Example 61: Synthesis of (R)-N-(4-(3-((5-methylpyrazin-2-yl)amino)pyrrolidine-1-carbonyl)phenyl)acrylamide

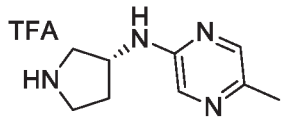


Step 1: (R)-tert-butyl 3-((5-methylpyrazin-2-yl)amino)pyrrolidine-1-carboxylate



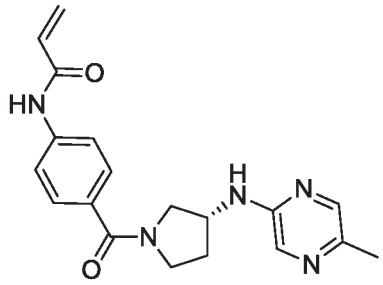
[00376] A mixture of 2-chloro-5-methylpyrazine (300 mg, 1.6 mmol), (R)-tert-butyl 3-aminopyrrolidine-1-carboxylate (206 mg, 1.6 mmol), BINAP (199 mg, 0.3 mmol), $Pd_2(dba)_3$ (73 mg, 0.08 mmol) and t-BuONa (307 mg, 3.2 mmol) in toluene (10 mL) was stirred at 80°C under N_2 for 3 hours. The mixture was cooled to RT and concentrated. The residue was purified by reverse phase chromatography to afford (R)-tert-butyl 3-((5-methylpyrazin-2-yl)amino)pyrrolidine-1-carboxylate (240 mg, 54%) as yellow oil. [M+H] Calc'd for $C_{14}H_{22}N_4O_2$, 279.1; Found, 279.1.

Step 2: (R)-5-methyl-N-(pyrrolidin-3-yl)pyrazin-2-amine 2,2,2-trifluoroacetate



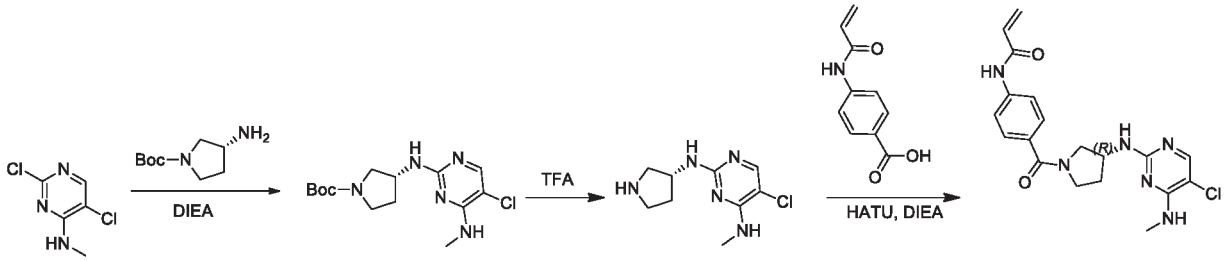
[00377] The title compound was prepared in 100% yield from (R)-tert-butyl 3-((5-methylpyrazin-2-yl)amino)pyrrolidine-1-carboxylate using general procedure of (R)-5-chloro-4-methyl-N-(pyrrolidin-3-yl)pyrimidin-2-amine 2,2,2-trifluoroacetate. [M+H] Calc'd for $C_9H_{14}N_4$, 179.1; Found, 179.1.

Step 3: (R)-N-(4-(3-((5-methylpyrazin-2-yl)amino)pyrrolidine-1-carbonyl)phenyl)acrylamide

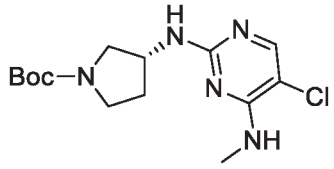


[00378] The title compound was prepared in 25% yield from (R)-5-methyl-N-(pyrrolidin-3-yl)pyrazin-2-amine 2,2,2-trifluoroacetate using general procedure of (R)-N-(4-(3-((5-chloro-4-methylpyrimidin-2-yl)amino)pyrrolidine-1-carbonyl)phenyl)acrylamide. ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.88-1.95 (m, 1H), 2.13-2.26 (m, 4H), 3.37-3.41 (m, 1H), 3.52-3.68 (m, 2H), 3.76-3.83 (m, 1H), 4.22-4.36 (m, 1H), 5.78 (d, J = 10.4 Hz, 1H), 6.27 (d, J = 16.8 Hz, 1H), 6.40-6.47 (m, 1H), 7.04-7.09 (m, 1H), 7.48-7.54 (m, 2H), 7.68-7.76 (m, 2H), 7.83-7.87 (m, 2H), 10.29 (s, 1H). [M+H] Calc'd for $C_{19}H_{21}N_5O_2$, 352.1; Found, 352.1.

Example 62: Synthesis of (R)-N-(4-(3-((5-chloro-4-(methylamino)pyrimidin-2-yl)amino)pyrrolidine-1-carbonyl)phenyl)acrylamide

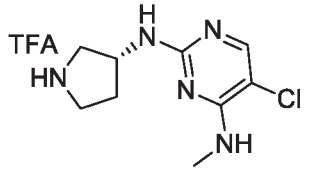


Step 1: (R)-tert-butyl 3-((5-chloro-4-(methylamino)pyrimidin-2-yl)amino)pyrrolidine-1-carboxylate



[00379] The title compound was prepared in 39% yield from 2,5-dichloro-N-methylpyrimidin-4-amine using general procedure of (R)-tert-butyl 3-((5-chloro-4-methylpyrimidin-2-yl)amino)pyrrolidine-1-carboxylate. [M+H] Calc'd for $C_{14}H_{22}ClN_5O_2$, 328.1; Found, 328.1.

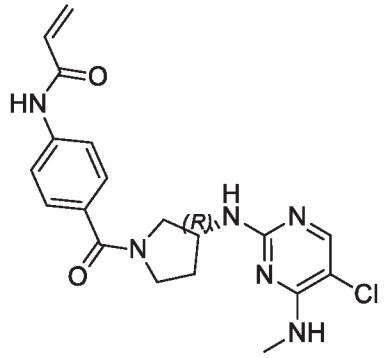
Step 2: (R)-5-chloro-N4-methyl-N2-(pyrrolidin-3-yl)pyrimidine-2,4-diamine



[00380] The title compound was prepared in 100% yield from (R)-tert-butyl 3-((5-chloro-4-(methylamino)pyrimidin-2-yl)amino)pyrrolidine-1-carboxylate using general procedure of (R)-5-

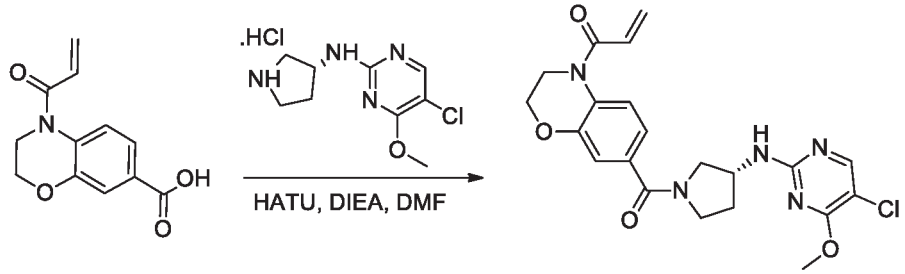
chloro-4-methyl-N-(pyrrolidin-3-yl)pyrimidin-2-amine 2,2,2-trifluoroacetate. [M+H] Calc'd for $C_9H_{14}ClN_5$, 228.0; Found, 228.0.

Step 3: (R)-N-(4-(3-((5-chloro-4-(methylamino)pyrimidin-2-yl)amino)pyrrolidine-1-carbonyl)phenyl)acrylamide



[00381] The title compound was prepared in 21% yield from (R)-5-chloro-N^4-methyl-N^2-(pyrrolidin-3-yl)pyrimidine-2,4-diamine 2,2,2-trifluoroacetate using general procedure of (R)-N-(4-(3-((5-chloro-4-methylpyrimidin-2-yl)amino)pyrrolidine-1-carbonyl)phenyl)acrylamide. ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.86-2.00 (m, 1H), 2.07-2.17 (m, 1H), 2.74 (s, 1.5H), 2.85 (s, 1.5H), 3.39-3.75 (m, 4H), 4.18-4.22 (m, 0.5H), 4.36-4.40 (m, 0.5H), 5.78 (d, J = 10.4 Hz, 1H), 6.26-6.30 (m, 1H), 6.41-6.48 (m, 1H), 6.89-7.05 (m, 2H), 7.48-7.54 (m, 2H), 7.69-7.77 (m, 3H), 10.32 (s, 1H). [M+H] Calc'd for $C_{19}H_{21}ClN_6O_2$, 401.1; Found, 401.1.

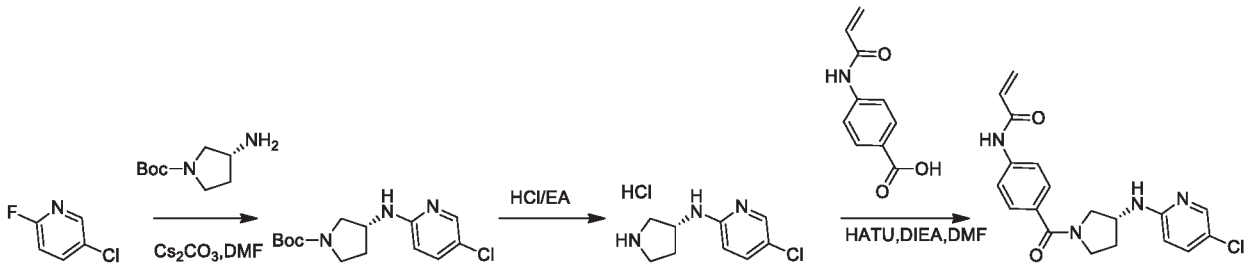
Example 63: Synthesis of (R)-1-(7-(3-((5-chloro-4-methoxypyrimidin-2-yl)amino)pyrrolidine-1-carbonyl)-2H-benzo[b][1,4]oxazin-4(3H)-yl)prop-2-en-1-one



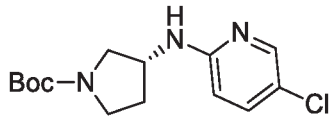
[00382] A mixture of 4-acryloyl-3,4-dihydro-2H-benzo[b][1,4]oxazine-7-carboxylic acid (150 mg, 0.64 mmol), (R)-5-chloro-4-methoxy-N-(pyrrolidin-3-yl)pyrimidin-2-amine hydrochloride (232 mg, 0.71 mmol), HATU (292 mg, 0.77 mmol) and DIEA (248 mg, 1.92 mmol) in DMF (20 mL) was stirred at RT overnight. The mixture was diluted with water (20 mL) and extracted with EA (20 mL* 3). The combined organic layer was washed with brine (20 mL), dried over Na_2SO_4, filtered and concentrated *in vacuo*. The residue was purified by prep-HPLC to afford (R)-1-(7-(3-((5-chloro-4-methoxypyrimidin-2-yl)amino)pyrrolidine-1-carbonyl)-2H-benzo[b][1,4]oxazin-4(3H)-yl)prop-2-en-1-one (89.9 mg, 32%) as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.91-2.13 (m, 2H), 3.50-3.95 (m, 9H), 4.30-4.31 (m, 3H), 5.83-5.85 (m, 1H), 6.25-6.30 (m, 1H), 6.78-6.79

(m, 1H), 7.02-7.08 (m, 2H), 7.49-7.67 (m, 2H), 8.08-8.14 (m, 1H). [M+H] Calc'd for $C_{21}H_{22}ClN_5O_4$, 444.1; Found, 444.1.

Example 64: Synthesis of (*R*)-*N*-(4-(3-((5-chloropyridin-2-yl)amino)pyrrolidine-1-carbonyl)phenyl)acrylamide

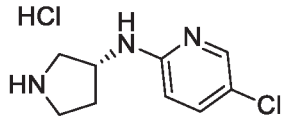


Step 1: (R)-tert-butyl 3-((5-chloropyridin-2-yl)amino)pyrrolidine-1-carboxylate



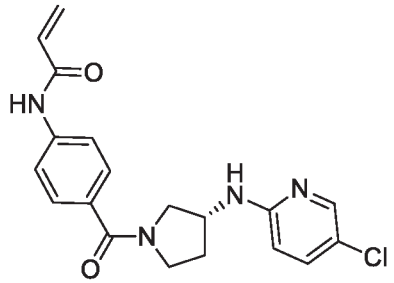
[00383] A mixture of 5-chloro-2-fluoropyridine (424 mg, 2.28 mmol), (*R*)-*tert*-butyl 3-aminopyrrolidine-1-carboxylate (300 mg, 2.28 mmol) and Cs_2CO_3 (1486 mg, 4.56 mmol) in DMF (2 mL) was stirred at 120 °C for 14 hours. The mixture was cooled to RT and concentrated. The residue was purified by flash chromatography on silica gel (petroleum ether/EtOAc = 5/1) to afford (R)-tert-butyl 3-((5-chloropyridin-2-yl)amino)pyrrolidine-1-carboxylate (150 mg, 22%) as a white solid. [M+H] Calc'd for $C_{14}H_{20}ClN_3O_2$, 298.1; Found, 298.1.

Step 2: (R)-5-chloro-N-(pyrrolidin-3-yl)pyridin-2-amine hydrochloride



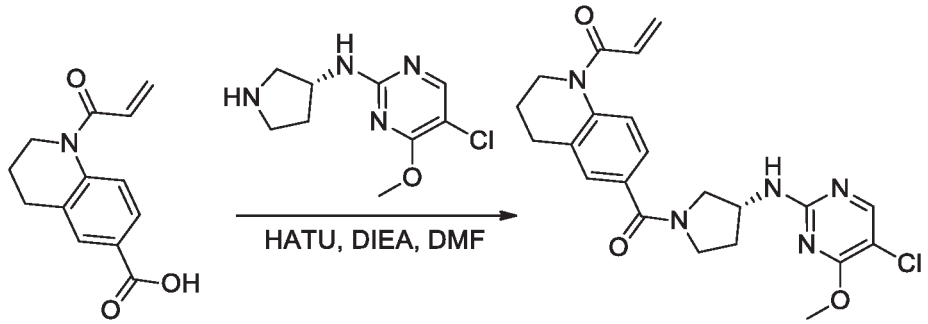
[00384] The title compound was prepared in 100% yield from (R)-tert-butyl 3-((5-chloropyridin-2-yl)amino)pyrrolidine-1-carboxylate using general procedure of (*R*)-5-chloro-4-methyl-*N*-(pyrrolidin-3-yl)pyridin-2-amine hydrochloride. [M+H] Calc'd for $C_9H_{12}ClN_3$, 198.0; Found, 198.0.

Step 3: (R)-N-(4-(3-((5-chloropyridin-2-yl)amino)pyrrolidine-1-carbonyl)phenyl)acrylamide



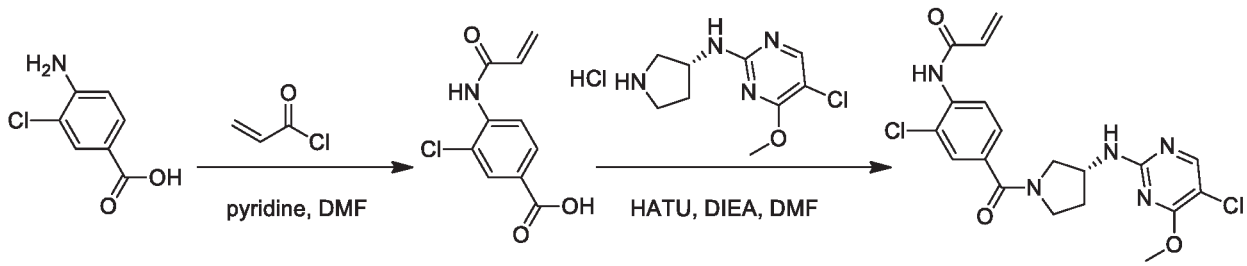
[00385] The title compound was prepared in 11% yield from (R)-5-chloro-N-(pyrrolidin-3-yl)pyridin-2-amine hydrochloride using general procedure of (R)-N-(4-(3-((5-chloro-4-methylpyrimidin-2-yl)amino)pyrrolidine-1-carbonyl)phenyl)acrylamide. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.96-2.01 (m, 1H), 2.25-2.50 (m, 1H), 3.37-3.96 (m, 4H), 4.34-4.37 (m, 1H), 4.52-4.60 (m, 1H), 5.79 (d, J = 10.4 Hz, 1H), 6.24-6.33 (m, 1H), 6.39-6.47 (m, 1H), 7.32-7.40 (m, 1H), 7.43-7.70 (m, 5H), 7.98 (s, 0.5H), 8.05 (s, 0.5H). [M+H] Calc'd for $C_{19}H_{19}ClN_4O_2$, 371.1; Found, 371.1.

Example 65: Synthesis of (R)-1-(6-(3-((5-chloro-4-methoxypyrimidin-2-yl)amino)pyrrolidine-1-carbonyl)-3,4-dihydroquinolin-1(2H)-yl)prop-2-en-1-one

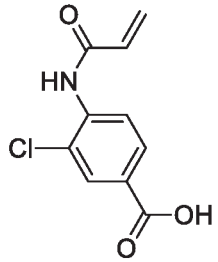


[00386] The title compound was prepared in 18% yield from 1-acryloyl-1,2,3,4-tetrahydro-quinoline-6-carboxylic acid using general procedure of (R)-N-(4-(3-((5-chloro-4-methylpyrimidin-2-yl)amino)pyrrolidine-1-carbonyl)phenyl)acrylamide. ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.88-2.15 (m, 4H), 2.72-2.73 (m, 2H), 3.28-3.94 (m, 9H), 4.29-4.45 (m, 1H), 5.72 (d, J = 12.0 Hz, 1H), 6.22 (d, J = 8.8 Hz, 1H), 6.57 (d, J = 16.8 Hz, 1H), 7.35 (m, 3H), 7.67 (m, 1H), 8.11 (s, 1H). [M+H] Calcd.: 442, Found: 442.

Example 66: Synthesis of (R)-N-(2-chloro-4-(3-((5-chloro-4-methoxypyrimidin-2-yl)amino)pyrrolidine-1-carbonyl)phenyl)acrylamide

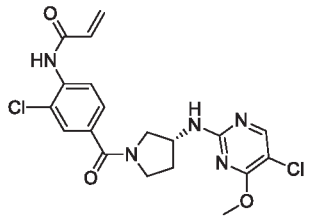


Step 1: 4-acrylamido-3-chlorobenzoic acid



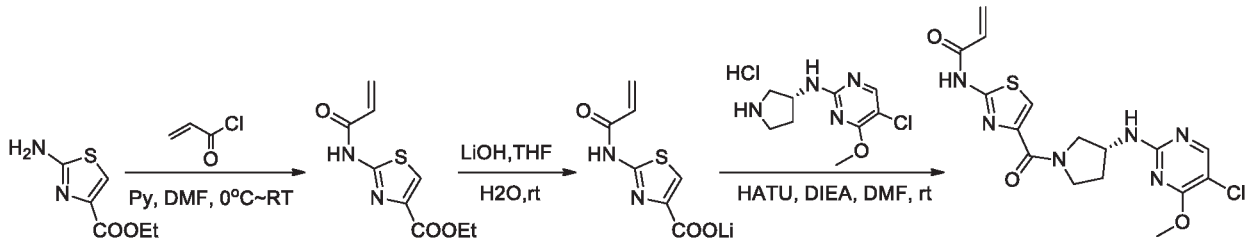
[00387] A mixture of 4-amino-3-chlorobenzoic acid (4.0 g, 23.3 mmol) in DMF (30 mL) was added Pyridine (3.6 g, 45.6 mmol) at 0 °C and then acryloyl chloride (2.1 g, 23.2 mmol). The reaction mixture was stirred at RT for 16h. The mixture was concentrated and added DCM (100 mL), washed with 0.5N HCl (30 mL), dried over Na_2SO_4, filtered and concentrated *in vacuo* to afford 4-acrylamido-3-chlorobenzoic acid (770 mg, 11%) as yellow solid. [M+H] Calc'd for $C_{10}H_8ClNO_3$, 226.1; Found, 226.1

Step 2: (R)-N-(2-chloro-4-(3-((5-chloro-4-methoxypyrimidin-2-yl)amino)pyrrolidine-1-carbonyl)phenyl)acrylamide

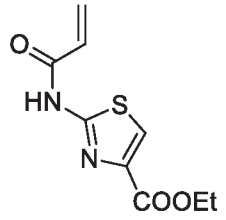


[00388] A mixture of 4-acrylamido-3-chlorobenzoic acid (150 mg, 0.67 mmol), (R)-5-chloro-4-methoxy-N-(pyrrolidin-3-yl)pyrimidin-2-amine hydrochloride (235 mg, 0.73 mmol), HATU (305 mg, 0.8 mmol) and DIEA (260 mg, 2.01 mmol) in DMF (15 mL) was stirred at RT overnight. The mixture was concentrated and purified by *prep*-HPLC to afford (R)-N-(2-chloro-4-(3-((5-chloro-4-methoxypyrimidin-2-yl)amino)pyrrolidine-1-carbonyl)phenyl)acrylamide (130.1 mg, 44%) as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.90-2.14 (m, 2H), 3.29-3.94 (m, 7H), 4.27-4.44 (m, 1H), 5.80-5.82 (m, 1H), 6.28-6.32 (m, 1H), 6.62-6.69 (m, 1H), 7.50-7.51 (m, 1H),7.62-7.67 (m, 2H), 7.89-7.91 (m, 1H), 8.08-8.14 (m, 1H), 9.79-9.80 (m, 1H). [M+H] Calc'd for $C_{19}H_{19}Cl_2N_5O_3$, 436.1; Found, 436.1.

<u>Example 67: Synthesis of (R)-N-(4-(3-((5-chloro-4-methoxypyrimidin-2-yl)amino)pyrrolidine-1-carbonyl)thiazol-2-yl)acrylamide</u>

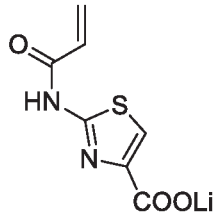


Step 1: ethyl 2-acrylamidothiazole-4-carboxylate



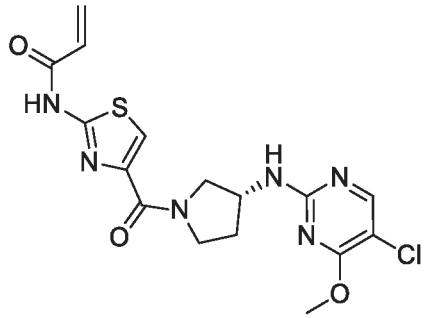
[00389] To a solution of ethyl 2-aminothiazole-4-carboxylate (5.0 g, 29.0 mmol) in DMF (35 mL) was added pyridine (2.5 mL) at 0°C. Then to the mixture was added acryloyl chloride (3.5 mL, 43.6 mmol) dropwise over 3 min. The mixture was stirred at RT overnight. The reaction was quenched with water (50 mL) and extracted with EA (50 mL*3). The combined organic layers were washed with water (100 mL*2) and brine (100 mL), dried over Na_2SO_4, filtered and concentrated *in vacuo*. The residue was purified by flash chromatography on silica gel (PE/EA = 1/1) to give ethyl 2-acrylamidothiazole-4-carboxylate (1.5 g, 23%). [M+H] Calcd.: 227, Found: 227.

Step 2: 2-acrylamidothiazole-4-carboxylic acid



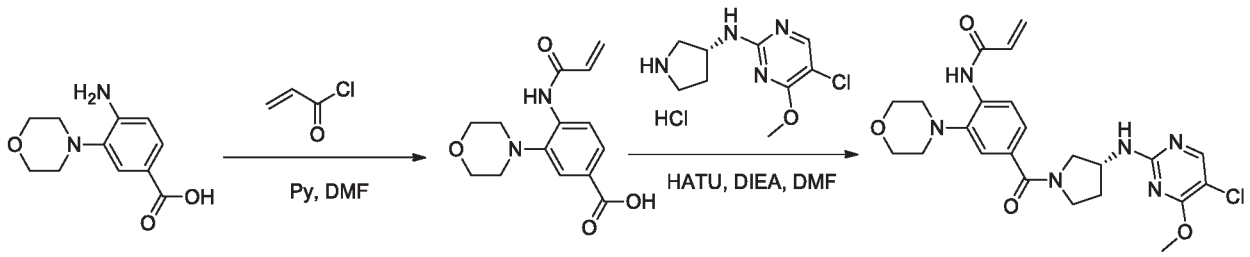
[00390] To a solution of 2-acrylamidothiazole-4-carboxylate (500 mg, 2.22 mmol) in THF (15 mL) and water (15mL) was added $LiOH.H_2O$ (93 mg, 2.22 mmol) at rt. The mixture was stirred at RT overnight. The reaction was concentrated *in vacuo* to give lithium 2-acrylamidothiazole-4-carboxylate (400 mg, 23%). [M+H] Calcd.: 199, Found: 199.

Step 3: (R)-N-(4-(3-((5-chloro-4-methoxypyrimidin-2-yl)amino)pyrrolidine-1-carbonyl)thiazol-2-yl)acrylamide

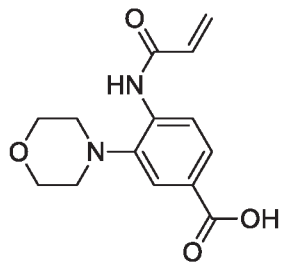


[00391] The title compound was prepared in 14% yield from Lithium salt of 2-Acryloylamino-thiazole-4-carboxylic acid using general procedure of (R)-N-(4-(3-((5-chloro-4-methylpyrimidin-2-yl)amino)pyrrolidine-1-carbonyl)phenyl)acrylamide. ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.99-2.02 (m, 1H), 2.10-2.15 (m, 1H), 3.67-3.69 (m, 3H), 3.97-4.00 (m, 3H), 4.10-4.40 (m, 2H), 5.89-5.92 (m, 1H), 6.40 (d, J = 10.0 Hz, 1H), 6.51-6.52 (m, 1H), 7.67 (s, 1H), 7.75 (s, 1H), 8.12 (d, J = 10.0 Hz, 1H), 12.39 (s, 1H). [M+H] Calcd.: 409, Found: 409.

Example 68: Synthesis of (R)-N-(4-(3-((5-chloro-4-methoxypyrimidin-2-yl)amino)pyrrolidine-1-carbonyl)-2-morpholinophenyl)acrylamide

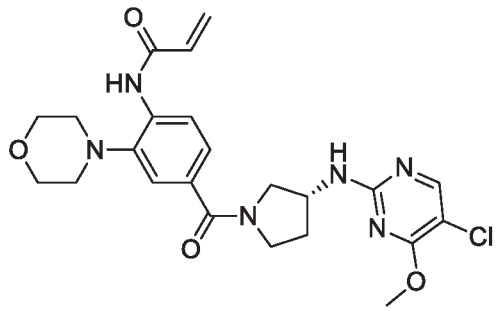


Step 1: 4-acrylamido-3-morpholinobenzoic acid



[00392] To a mixture of 4-amino-3-morpholinobenzoic acid (500 mg, 2.25 mmol) in DMF (20 mL) was added Pyridine (533 mg, 6.75 mmol) and acryloyl chloride (610 mg, 6.75 mmol) at 0°C. The mixture was stirred at RT for 5 h. The mixture was then concentrated and purified by column to afford 4-acrylamido-3-morpholinobenzoic acid (170 mg, 27%) as a white solid. [M+H] Calc'd for $C_{14}H_{17}N_2O_4$, 277.1; Found, 277.1.

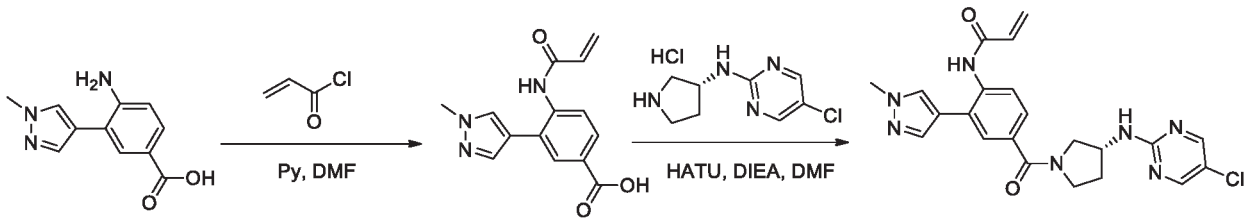
Step 2: (R)-N-(4-(3-((5-chloro-4-methoxypyrimidin-2-yl)amino)pyrrolidine-1-carbonyl)-2-morpholinophenyl)acrylamide



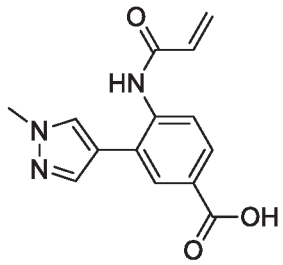
[00393] A mixture of 4-acrylamido-3-morpholinobenzoic acid (150 mg, 0.54 mmol), (R)-5-chloro-4-methoxy-N-(pyrrolidin-3-yl)pyrimidin-2-amine (HCl salt) (193 mg, 0.59 mmol), HATU (246 mg, 0.65 mmol) and DIEA (209 mg, 1.62 mmol) in DMF (10 mL) was stirred at RT overnight. The mixture was diluted with water (10 mL) and extracted with DCM (10 mL* 3). The combined organic layer was washed with brine (20 mL), dried over Na_2SO_4, filtered and concentrated *in vacuo*. The residue was purified by *prep*-HPLC to afford (R)-N-(4-(3-((5-chloro-4-methoxypyrimidin-2-yl)amino)pyrrolidine-1-carbonyl)-2-morpholinophenyl)acrylamide (101 mg, 38%) as a white solid (TFA salt). ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.93-2.09 (m, 1H), 2.09-2.31 (m, 1H), 2.78-2.83 (m, 4H), 3.41-3.45 (m, 1H), 3.50-3.55 (m, 1H), 3.62-3.69 (m, 1H), 3.79-3.95 (m, 8H), 4.26-4.30 (m, 1H), 5.79 (d, J = 10.4 Hz, 1H), 6.25 (s, 0.5H), 6.29 (s, 0.5H), 6.65-6.73 (m,

1H), 7.25-7.34 (m, 2H), 7.73 (br s, 1H), 8.05-8.15 (m, 2H), 9.20 (s, 0.5H), 9.22(s, 0.5H). [M+H] Calc'd for $C_{23}H_{28}ClN_6O_4$, 487.1; Found, 487.

Example 69: Synthesis of (R)-N-(4-(3-((5-chloropyrimidin-2-yl)amino)pyrrolidine-1-carbonyl)-2-(1-methyl-1H-pyrazol-4-yl)phenyl)acrylamide

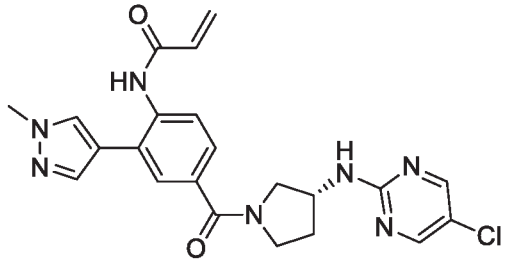


Step 1: 4-acrylamido-3-(1-methyl-1H-pyrazol-4-yl)benzoic acid



[00394] To a mixture of 4-amino-3-(1-methyl-1H-pyrazol-4-yl)benzoic acid (500 mg, 2.30 mmol) in DMF (20 mL) was added Pyridine (545 mg, 6.90 mmol) at 0°C followed by acryloyl chloride (312 mg, 3.45 mmol). The mixture was allowed to slowly warm to RT and stirred overnight. The mixture was then concentrated and purified by column chromatography to afford 4-acrylamido-3-(1-methyl-1H-pyrazol-4-yl)benzoic acid (150 mg, 24%) as white solid. [M+H] Calc'd for $C_{14}H_{14}N_3O_3$, 272.0; Found, 272.0

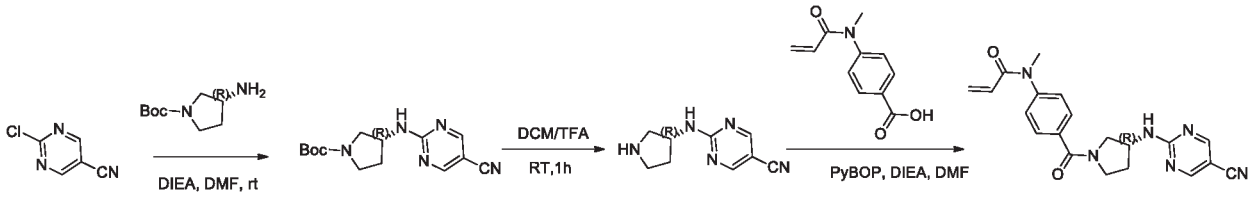
Step 2: (R)-N-(4-(3-((5-chloropyrimidin-2-yl)amino)pyrrolidine-1-carbonyl)-2-(1-methyl-1H-pyrazol-4-yl)phenyl)acrylamide



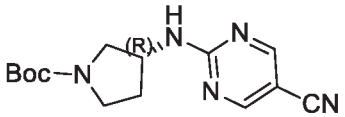
[00395] A mixture of 4-acrylamido-3-(1-methyl-1H-pyrazol-4-yl)benzoic acid (150 mg, 0.55 mmol), (R)-5-chloro-N-(pyrrolidin-3-yl)pyrimidin-2-amine (HCl salt) (155 mg, 0.66 mmol), HATU (250 mg, 0.66 mmol) and DIEA (212 mg, 1.65 mmol) in DMF (10 mL) was stirred at RT overnight. The mixture was diluted with water (10 mL) and extracted with DCM (10 mL* 3). The combined organic layer was washed with brine (20 mL), dried over Na_2SO_4, filtered and concentrated *in vacuo*. The residue was purified by *prep*-HPLC to afford (R)-N-(4-(3-((5-chloropyrimidin-2-

yl)amino)pyrrolidine-1-carbonyl)-2-(1-methyl-1H-pyrazol-4-yl)phenyl)acrylamide (96.2 mg, 39%) as a white solid (TFA salt). ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.88-2.01 (m, 1H), 2.11-2.19 (m, 1H), 3.37-3.46 (m, 1H), 3.64-3.67 (m, 1H), 3.74-3.80 (m, 2H), 3.85-3.88 (m, 3H), 4.21-4.42 (m, 1H), 5.75 (d, J = 10.0 Hz, 1H), 6.22 (s, 0.5H), 6.26 (s, 0.5H), 6.48-6.55 (m, 1H), 7.35-7.40 (m, 1H), 7.54-7.68 (m, 3H), 7.81 (br s, 1H), 7.98 (d, J = 8.4 Hz, 1H), 8.31 (s, 1H), 8.38 (s, 1H), 9.61 (s, 0.5H), 9.62(s, 0.5H) . [M+H] Calc'd for $C_{22}H_{23}ClN_7O_2$, 452.1; Found, 452.1

Example 70: Synthesis of (R)-N-(4-(3-((5-cyanopyrimidin-2-yl)amino)pyrrolidine-1-carbonyl)phenyl)-N-methylacrylamide

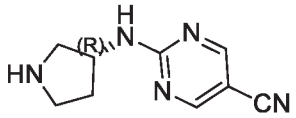


Step 1: (*R*)-tert-butyl 3-((5-cyanopyrimidin-2-yl)amino)pyrrolidine-1-carboxylate



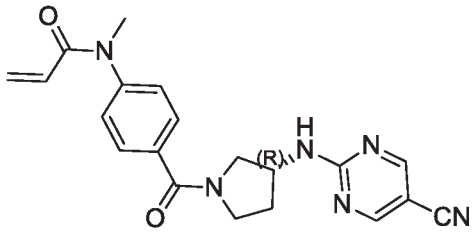
[00396] A mixture of 2-chloropyrimidine-5-carbonitrile (2.0 g, 14.3 mmol), (R)-tert-butyl 3-aminopyrrolidine-1-carboxylate (2.7 g, 14.3 mmol) and DIEA (4.6 g, 35.8 mmol) in DMF (20 mL) was stirred at rt overnight. The solution was poured into water (50 mL) and was extracted with DCM (50 mL*2). The combined organic layers were washed with water (100 mL*2) and brine (100 mL), dried over Na_2SO_4, concentrated and purified by flash column chromatography (PE : EA = 10 : 1) to give (*R*)-*tert*-butyl 3-((5-cyanopyrimidin-2-yl)amino)pyrrolidine-1-carboxylate (4.1 g, 99%) as white solid. [M+H] MS Calc'd: $C_{14}H_{19}N_5O_2$, 290.2, Found: 290.2.

Step 2: (*R*)-2-(pyrrolidin-3-ylamino)pyrimidine-5-carbonitrile



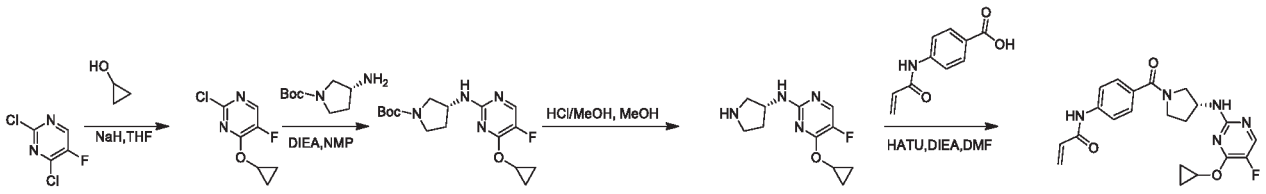
[00397] To a solution of (*R*)-*tert*-butyl 3-((5-cyanopyrimidin-2-yl)amino)pyrrolidine-1-carboxylate (2.0 g, 6.9 mmol) in DCM (15 mL) was added TFA (5 mL) at rt. The mixture was stirred at rt for 1h and concentrated *in vacuo* to give crude product. DCM (20 mL) was added to the crude product and the reaction mixture was washed with sodium carbonate aqueous solution. The organics were dried over anhydrous sodium sulfate, filtered and concentrated *in vacuo* to give (R)-2-(pyrrolidin-3-ylamino)pyrimidine-5-carbonitrile (1.3 g, 100%) as an off-white solid. [M+H] MS Calc'd: $C_9H_{11}N_5$, 190.1; Found: 190.1.

Step 3: (R)-N-(4-(3-((5-cyanopyrimidin-2-yl)amino)pyrrolidine-1-carbonyl)phenyl)-N-methylacrylamide

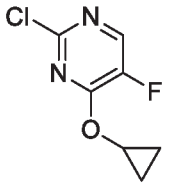


[00398] A mixture of 4-(N-methylacrylamido)benzoic acid (196 mg, 0.95 mmol), (R)-2-(pyrrolidin-3-ylamino)pyrimidine-5-carbonitrile (200 mg, 1.06 mmol), PyBOP (551 mg, 1.06 mmol) and DIEA (680 mg, 5.30 mmol) in DMF (15 mL) was stirred at rt for 3 h. The reaction mixture was concentrated *in vacuo*. The residue was purified by *prep*-HPLC to give (R)-N-(4-(3-((5-cyanopyrimidin-2-yl)amino)pyrrolidine-1-carbonyl)phenyl)-N-methylacrylamide (161.8 mg, 40.7%) as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6): 1.94-2.06 (m, 1H), 2.17-2.25 (m, 1H), 3.30 (d, J = 4.4 Hz, 3H), 3.39-3.87 (m, 4H), 4.24-4.58 (m, 1H), 5.61-5.65 (m, 1H), 6.13-6.24 (m, 2H), 7.37 (t, J = 11.6 Hz, 2H), 7.63 (t, J = 10.4 Hz, 2H), 8.67-8.81 (m, 3H). [M+H] Ms Calc'd: $C_{20}H_{20}N_6O_2$, 377.2; Found, 377.1.

Example 71: Synthesis of (*R*)-*N*-(4-(3-((4-cyclopropoxy-5-fluoropyrimidin-2-yl)amino)pyrrolidine-1-carbonyl)phenyl)acrylamide

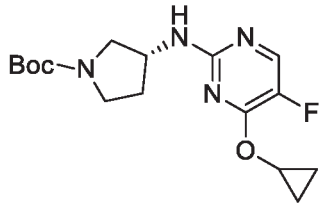


Step 1: 2-chloro-4-cyclopropoxy-5-fluoropyrimidine



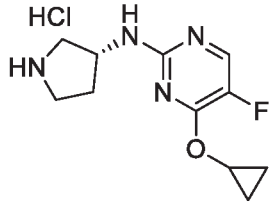
[00399] The title compound was prepared in 100% yield from 2,4-dichloro-5-fluoropyrimidine using general procedure of 2-chloro-4-cyclopropoxy-5-methylpyrimidine. [M+H] Calc'd for $C_7H_6ClFN_2O$, 189.0; Found, 189.0.

Step 2: (R)-tert-butyl 3-((4-cyclopropoxy-5-fluoropyrimidin-2-yl)amino)pyrrolidine-1-carboxylate



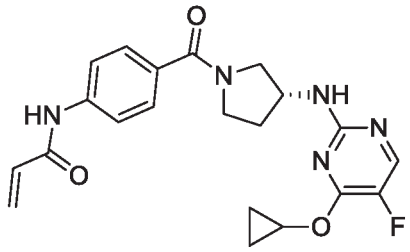
[00400] The title compound was prepared in 53% yield from 2-chloro-4-cyclopropoxy-5-fluoropyrimidine using general procedure of (*R*)-*tert*-butyl 3-((5-chloro-4-methylpyrimidin-2-yl)amino)pyrrolidine-1-carboxylate. [M+H] Calc'd for $C_{16}H_{23}FN_4O_3$, 339.1; Found, 339.1.

Step 3: (R)-4-cyclopropoxy-5-fluoro-N-(pyrrolidin-3-yl)pyrimidin-2-amine



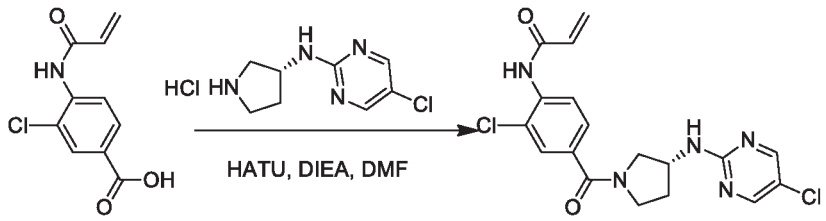
[00401] The title compound was prepared in 100% yield from (*R*)-*tert*-butyl 3-((4-cyclopropoxy-5-fluoropyrimidin-2-yl)amino)pyrrolidine-1-carboxylate using general procedure of (*R*)-5-chloro-4-cyclopropoxy-*N*-(pyrrolidin-3-yl)pyrimidin-2-amine hydrochloride. [M+H] Calc'd for $C_{11}H_{15}FN_4O$, 239.1; Found, 239.1.

Step 4: (R)-N-(4-(3-((4-cyclopropoxy-5-fluoropyrimidin-2-yl)amino)pyrrolidine-1-carbonyl)phenyl)acrylamide



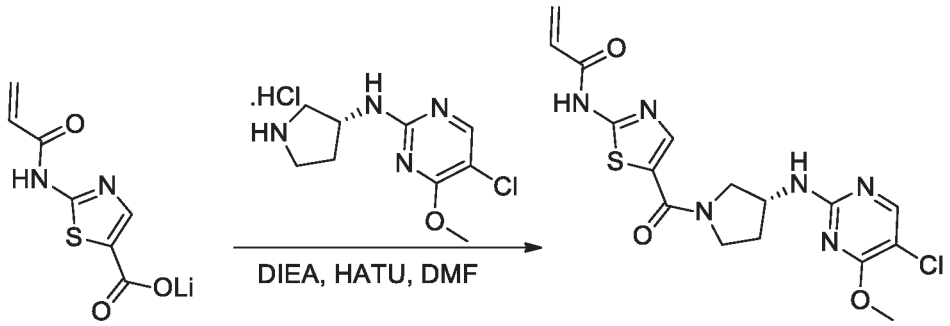
[00402] The title compound was prepared in 21% yield from (R)-4-cyclopropoxy-5-fluoro-N-(pyrrolidin-3-yl)pyrimidin-2-amine hydrochloride using general procedure of (*R*)-*N*-(4-(3-((5-chloro-4-methylpyrimidin-2-yl)amino)pyrrolidine-1-carbonyl)phenyl)acrylamide. ^{1}H NMR (400 MHz, DMSO-d_6): δ 0.61-0.78 (m, 4H), 1.99-2.07 (m, 1H), 2.13-2.17 (m, 1H), 3.42-3.85 (m, 4H), 4.14-4.40 (m, 2H), 5.77-5.80 (m, 1H), 6.26-6.31 (m, 1H), 6.41-6.48 (m, 1H), 7.46-7.54 (m, 3H), 7.69-7.73 (m, 2H), 8.06 (d, J = 2.8 Hz, 0.5H), 8.13 (d, J = 2.4 Hz, 0.5H), 10.31 (s, 1H). [M+H] Calc'd for $C_{21}H_{22}FN_5O_3$, 412.1; Found, 412.1.

Example 72: Synthesis of (R)-N-(2-chloro-4-(3-((5-chloropyrimidin-2-yl)amino)pyrrolidine-1-carbonyl)phenyl)acrylamide



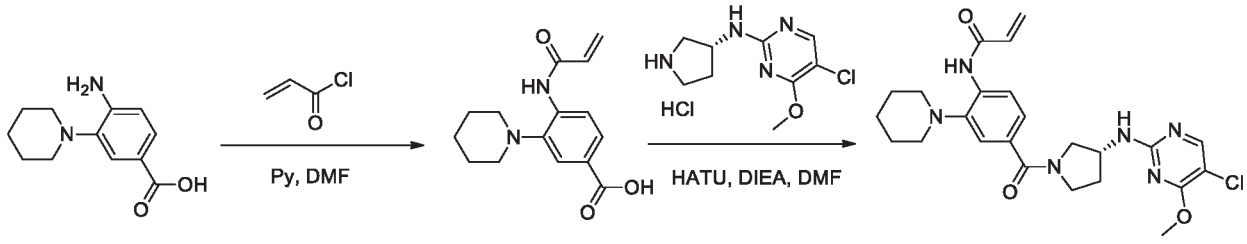
[00403] A mixture of 4-acrylamido-3-chlorobenzoic acid (300 mg, 1.34 mmol), (R)-5-chloro-N-(pyrrolidin-3-yl)pyrimidin-2-amine hydrochloride (354 mg, 1.46 mmol), HATU (610 mg, 1.6 mmol) and DIEA (520 mg, 4.02 mmol) in DMF (20 mL) was stirred at RT for overnight. The mixture was concentrated and purified by prep-HPLC to afford (R)-N-(2-chloro-4-(3-((5-chloropyrimidin-2-yl)amino)pyrrolidine-1-carbonyl)phenyl)acrylamide (38.3 mg, 5.5%) as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.98-2.14 (m, 2H), 3.38-3.74 (m, 4H), 4.27-4.42 (m, 1H), 5.80-5.82 (m, 1H), 6.27-6.32 (m, 1H), 6.64-6.69 (m, 1H), 7.48-7.49 (m, 1H),7.62-7.66 (m, 2H), 7.82-7.91 (m, 1H), 8.32-8.38 (m, 2H), 9.78-9.80 (m, 1H). [M+H] Calc'd for $C_{18}H_{17}Cl_2N_5O_2$, 406.1; Found, 406.1.

Example 73: Synthesis of (R)-N-(5-(3-((5-chloro-4-methoxypyrimidin-2-yl)amino)pyrrolidine-1-carbonyl)thiazol-2-yl)acrylamide

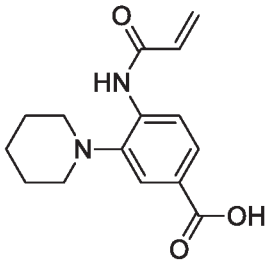


[00404] The title compound was prepared in 2% yield from lithium 2-acrylamidothiazole-5-carboxylate using general procedure of (R)-N-(4-(3-((5-chloro-4-methylpyrimidin-2-yl)amino)pyrrolidine-1-carbonyl)phenyl)acrylamide.^{1}H NMR (400 MHz, DMSO-d_6): δ 1.98-2.25 (m, 2H), 3.52-3.92 (m, 6H), 3.97-4.08 (m, 1H), 4.38-4.43 (m, 1H), 2.93-5.96 (m, 1H), 6.41-6.53 (m, 2H), 7.75 (brs, 1H), 7.94-7.99 (m, 1H), 8.14 (s, 1H), 12.59 (s, 1H). [M+H] Calcd.: 409.0, Found: 409.0.

Example 74: Synthesis of (R)-N-(4-(3-((5-chloro-4-methoxypyrimidin-2-yl)amino)pyrrolidine-1-carbonyl)-2-(piperidin-1-yl)phenyl)acrylamide

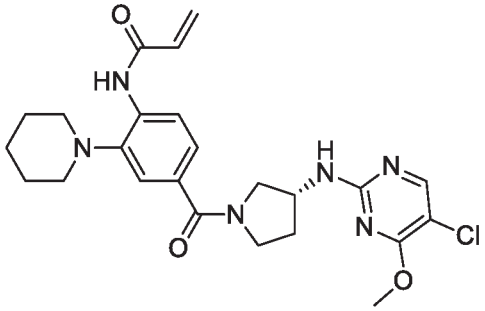


Step 1: 4-acrylamido-3-(piperidin-1-yl)benzoic acid



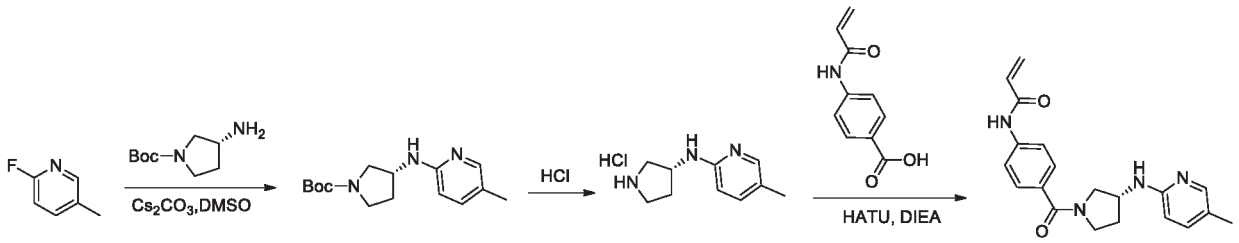
[00405] A mixture of 4-amino-3-(piperidin-1-yl)benzoic acid (1.0 g, 4.5 mmol) in DMF (20 mL) was added Pyridine (1.07 g, 13.6 mmol) followed by acryloyl chloride (1.23 g, 13.6 mmol) at 0°C. The mixture was then stirred at RT overnight. The mixture was concentrated and purified by column chromatography to afford 4-acrylamido-3-(piperidin-1-yl)benzoic acid (700 mg, 58%) as yellow oli. [M+H] Calc'd for $C_{15}H_{19}N_2O_3$, 275.1; Found, 275.1

Step 2: (R)-N-(4-(3-((5-chloro-4-methoxypyrimidin-2-yl)amino)pyrrolidine-1-carbonyl)-2-(piperidin-1-yl)phenyl)acrylamide

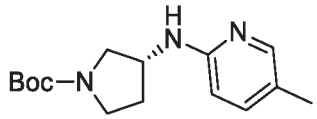


[00406] A mixture of 4-acrylamido-3-(piperidin-1-yl)benzoic acid (150 mg, 0.55 mmol), (R)-5-chloro-4-methoxy-N-(pyrrolidin-3-yl)pyrimidin-2-amine (HCl salt) (159 mg, 0.66 mmol), HATU (250 mg, 0.66 mmol) and DIEA (212 mg, 1.65 mmol) in DMF (10 mL) was stirred at RT for overnight. The mixture was diluted with water (10 mL) and extracted with DCM (10 mL* 3). The combined organic layer was then washed with brine (20 mL), dried over Na_2SO_4, filtered and concentrated *in vacuo*. The residue was purified by *prep*-HPLC to afford (R)-N-(4-(3-((5-chloro-4-methoxypyrimidin-2-yl)amino)pyrrolidine-1-carbonyl)-2-(piperidin-1-yl)phenyl)acrylamide (16 mg, 6%) as a white solid (TFA salt). ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.47-1.55 (m, 2H), 1.66-1.76 (m, 4H), 1.88-2.01 (m, 1H), 2.14-2.18 (m, 1H), 2.67-2.78 (m, 4H), 3.40-3.94 (m, 7H), 4.24-4.43 (m, 1H), 5.79 (d, J = 10.0 Hz, 1H), 6.24 (s, 0.5H), 6.28 (s, 0.5H), 6.63-6.71 (m, 1H), 7.21-7.31 (m, 2H), 7.71 (br s, 1H), 8.02-8.15 (m, 2H), 9.09 (s, 0.5H), 9.11 (s, 0.5H). [M+H] Calc'd for $C_{24}H_{30}ClN_6O_3$, 485.2; Found, 485.2.

Example 75: Synthesis of (*R*)-*N*-(4-(3-((5-methylpyridin-2-yl)amino)pyrrolidine-1-carbonyl)phenyl)acrylamide

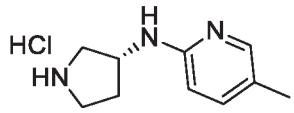


Step 1: (R)-tert-butyl 3-((5-methylpyridin-2-yl)amino)pyrrolidine-1-carboxylate



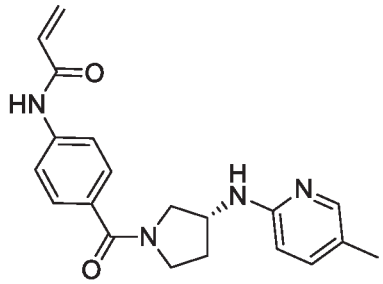
[00407] A mixture of 2-fluoro-5-methylpyridine (1006 mg, 5.4 mmol), (R)-tert-butyl 3-aminopyrrolidine-1-carboxylate (600 mg, 5.4 mmol) and Cs_2CO_3 (3520 mg, 10.8 mmol) in DMSO (2 mL) was stirred at 160°C for 32 hours. The mixture was cooled to RT, diluted with water (80 mL) and extracted with EtOAc (80 mL*3). The combined organic phase was washed with brine (50 mL), dried over Na_2SO_4, filtered and concentrated *in vacuo*. The residue was purified by flash chromatography on silica gel (petroleum ether/EtOAc = 5/1) to afford (*R*)-*tert*-butyl 3-((5-methylpyridin-2-yl)amino)pyrrolidine-1-carboxylate (60 mg, 4%) as a white solid. [M+H] Calc'd for $C_{15}H_{23}N_3O_2$, 278.1; Found, 278.1.

Step 2: (R)-5-methyl-N-(pyrrolidin-3-yl)pyridin-2-amine hydrochloride



[00408] To a mixture of (*R*)-*tert*-butyl 3-((5-methylpyridin-2-yl)amino)pyrrolidine-1-carboxylate (60 mg, 0.217 mmol) in EtOAc (2 mL) was added HCl/EtOAc (4M, 2 mL). The mixture was stirred at RT for 2 hours. The mixture was concentrated *in vacuo* to afford (*R*)-5-methyl-*N*-(pyrrolidin-3-yl)pyridin-2-amine hydrochloride (46 mg, crude, 100%) as a yellow solid. [M+H] Calc'd for $C_{10}H_{15}N_3$, 178.1; Found, 178.1.

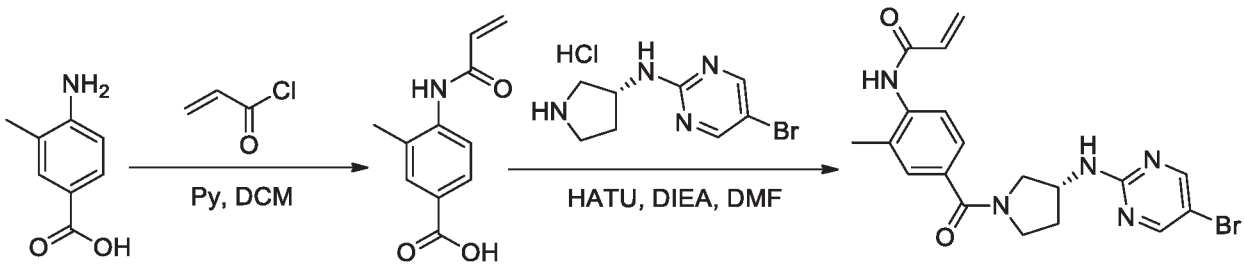
Step 3: (R)-N-(4-(3-((5-methylpyridin-2-yl)amino)pyrrolidine-1-carbonyl)phenyl)acrylamide



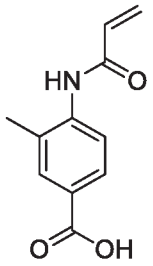
[00409] The title compound was prepared in 16% yield from (*R*)-5-methyl-*N*-(pyrrolidin-3-yl)pyridin-2-amine hydrochloride using general procedure of (*R*)-*N*-(4-(3-((5-chloro-4-methylpyrimidin-2-yl)amino)pyrrolidine-1-carbonyl)phenyl)acrylamide. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.92-2.00 (m,

1H), 2.15-2.25 (m, 3H), 2.31-2.36 (m, 1H), 3.34-3.57 (m, 1H), 3.64-4.04 (m, 3H), 4.32-4.47 (m, 2H), 5.79 (d, J = 10.0 Hz, 1H), 6.22-6.30 (m, 2H), 6.37-6.47 (m, 1H), 6.99-7.21 (m, 1H), 7.29-7.60 (m, 4H), 7.86 (s, 0.5H), 7.94 (s, 0.5H). [M+H] Calc'd for $C_{20}H_{22}N_4O_2$, 351.1; Found, 351.1.

Example 76: Synthesis of (R)-N-(4-(3-((5-bromopyrimidin-2-yl)amino)pyrrolidine-1-carbonyl)-2-methylphenyl)acrylamide

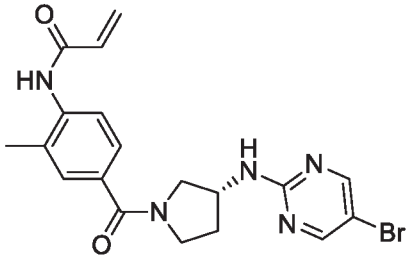


Step 1: 4-acrylamido-3-methylbenzoic acid



[00410] To a solution of 4-amino-3-methylbenzoic acid (10.0 g, 66.0 mmol) and Pyridine (16 mL) in DMF (50 mL) was added acryloyl chloride (6.0 g, 66.0 mmol) dropwise. The mixture was stirred at RT for 3h. The residue was diluted with water (100 mL) and extracted with DCM (100 mL* 3). The combined organic layer was washed with brine (200 mL), dried over Na_2SO_4, filtered and concentrated *in vacuo*. The residue was purified by column chromatography (PE:EA = 1:1) to afford 4-acrylamido-3-methylbenzoic acid (800 mg, 6%) as white solid. [M+H] Calc'd for $C_{11}H_{12}NO_3$, 206.0; Found, 206.0

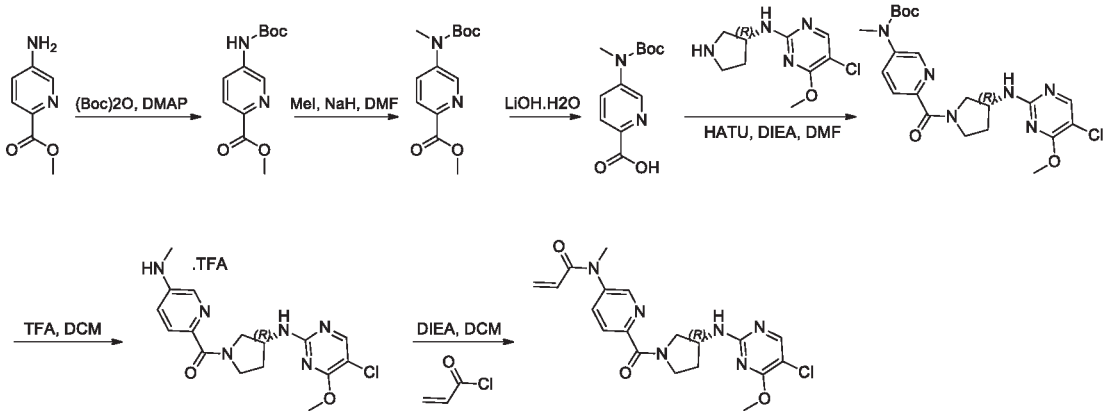
Step 2: (R)-N-(4-(3-((5-bromopyrimidin-2-yl)amino)pyrrolidine-1-carbonyl)-2-methylphenyl)acrylamide



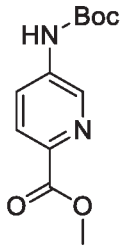
[00411] A mixture of 4-acrylamido-3-methylbenzoic acid (260 mg, 1.76 mmol), (R)-5-bromo-N-(pyrrolidin-3-yl)pyrimidin-2-amine (586 mg, 2.10 mmol), HATU (798 mg, 2.10 mmol) and DIEA (681 mg, 5.28 mmol) in DMF (20mL) was stirred at RT for overnight. The mixture was diluted with water (20 mL) and extracted with DCM (20 mL* 3). The combined organic layer was washed

with brine (30 mL), dried over Na_2SO_4, filtered and concentrated in-vacuo. The residue was purified by *prep*-HPLC to afford (R)-N-(4-(3-((5-bromopyrimidin-2-yl)amino)pyrrolidine-1-carbonyl)-2-methylphenyl)acrylamide (233.7 mg, 31%) as white solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.93-2.08 (m, 1H), 2.20-2.49 (m, 4H), 3.28-3.77 (m, 4H), 4.23-4.39 (m, 1H), 5.76 (d, J = 10.4 Hz, 1H), 6.23 (s, 0.5H), 6.28 (s, 0.5H), 6.53-6.60 (m, 1H), 7.30-7.40 (m, 2H), 7.59-7.64 (m, 1H), 7.79-7.82 (m, 1H), 8.36 (s, 1H), 8.42 (s, 1H), 9.51 (s, 0.5H), 9.56 (s, 0.5H). [M+H] Calc'd for $C_{19}H_{21}BrN_5O_2$, 430.0; Found, 430.0.

Example 77: Synthesis of (R)-N-(6-(3-((5-chloro-4-methoxypyrimidin-2-yl)amino)pyrrolidine-1-carbonyl)pyridin-3-yl)-N-methylacrylamide

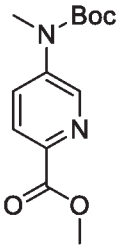


Step 1: methyl 5-((tert-butoxycarbonyl)amino)picolinate



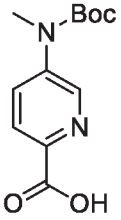
[00412] To a solution of 5-Amino-pyridine-2-carboxylic acid methyl ester (1.0 g, 6.6 mmol) in DCM (15 mL) was added DMAP (8 mg, 0.07 mmol) and $(Boc)_2O$ (1.6 g, 7.2 mmol) at ice-bath. The mixture was stirred at RT overnight. Then the reaction mixture was diluted with DCM (20 mL) and washed with water (20 mL). The organic phase was seperated, dried over Na_2SO_4, filtered and concentrated *in vacuo*. The residue was purified by flash chromatography on silica gel (petroleum ether/EtOAc = 2/1) to afford product (0.8 g, 48%) as a white solid. [M+H] MS Calcd.: $C_{12}H_{16}N_2O_4$, 253.1, Found: 253.1.

Step 2: methyl 5-((tert-butoxycarbonyl)(methyl)amino)picolinate



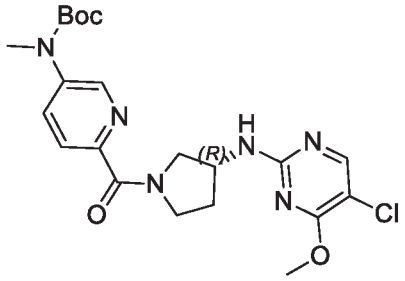
[00413] To a solution of methyl 5-((tert-butoxycarbonyl)(methyl)amino)picolinate (700 mg, 0.78 mmol) in DMF (15 mL) was added NaH (200 mg, 60%, 3.33 mmol) at 0 °C, and the mixture was stirred at 0 °C for 30 minutes. MeI was added and the mixture was stirred at rt overnight. The mixture was quenched with water (30 mL) and extracted with EA (30 mL*3). The combined organic layers were washed with water (30 mL*2) and brine (30 mL), dried over Na_2SO_4, filtered and concentrated *in vacuo*. The residue was purified by flash chromatography on silica gel (petroleum ether/EtOAc = 2/1) to afford product (150 mg, 48%) as a white solid. [M+H] MS Calcd.: $C_{13}H_{18}N_2O_4$, 267.1, Found: 267.1.

Step 3: 5-((tert-butoxycarbonyl)(methyl)amino)picolinic acid



[00414] To a solution of 5-(tert-butoxycarbonyl-methyl-amino)-pyridine-2-carboxylic acid methyl ester (150 mg, 0.56 mmol) in MeOH (5 mL) was added $LiOH.H_2O$ (71 mg, 1.69 mmol) and water (5 mL) at RT. The mixture was stirred at RT overnight. MeOH was concentrated *in vacuo*. The residue was acidated with 1 N HCl to pH 6, and extracted with EA (10 mL), the organic layer was dried over Na_2SO_4, filtered and concentrated *in vacuo* to afford product (120 mg, 80%) as a white solid. [M+H] MS Calcd.: $C_{12}H_{16}N_2O_4$, 253.1, Found: 253.1.

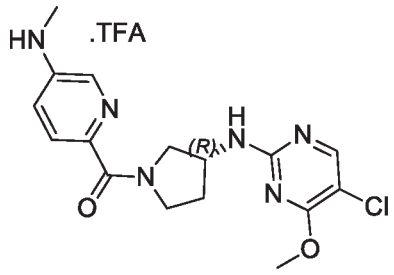
Step 4: (R)-tert-butyl (6-(3-((5-chloro-4-methoxypyrimidin-2-yl)amino)pyrrolidine-1-carbonyl)pyridin-3-yl)(methyl)carbamate



[00415] To a solution of 5-((tert-butoxycarbonyl)(methyl)amino)picolinic acid (120 mg, 0.48 mmol) in DMF (5 mL) was added (R)-5-chloro-4-methoxy-N-(pyrrolidin-3-yl)pyrimidin-2-amine (160 mg,

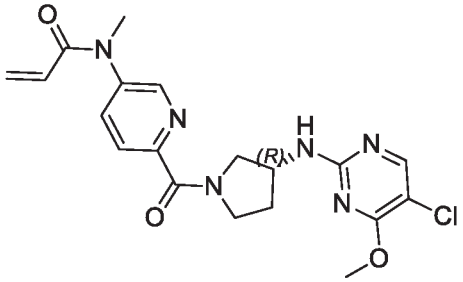
0.48 mmol) and DIEA (185 mg, 1.43 mmol) at rt. The mixture was stirred at rt 30 minutes and HATU (220 mg, 0.57 mmol) was then added. The mixture was stirred at RT overnight. The reaction was quenched with water (50 mL) and extracted with EA (30 mL*3). The combined organic layers were washed with water (30 mL*2) and brine (30 mL), dried over Na_2SO_4, filtered and concentrated *in vacuo*. The residue was purified by flash chromatography on silica gel (petroleum ether/EtOAc = 2/1) to afford the desired product (180 mg, 82%) as a white solid. [M+H] MS Calcd.: $C_{21}H_{27}ClN_6O_4$, 463.1, Found: 463.1.

Step 5: (R)-(3-((5-chloro-4-methoxypyrimidin-2-yl)amino)pyrrolidin-1-yl)(5-(methylamino)pyridin-2-yl)methanone TFA salt



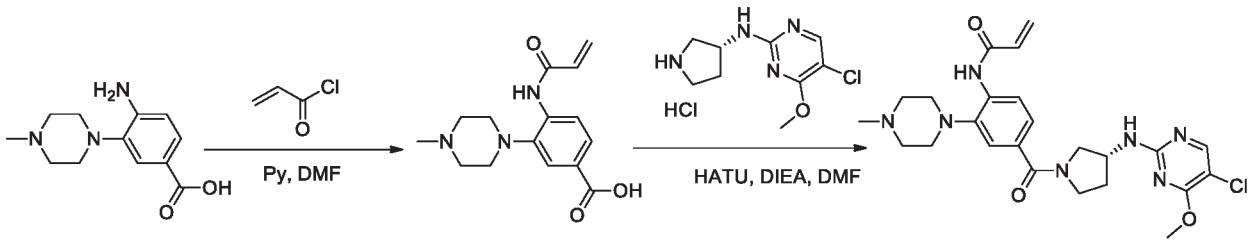
[00416] To a solution of (R)-tert-butyl (6-(3-((5-chloro-4-methoxypyrimidin-2-yl)amino)pyrrolidine-1-carbonyl)pyridin-3-yl)(methyl)carbamate (180 mg, 0.39 mmol) in DCM (5 mL) was added TFA (1 mL) at rt. The mixture was stirred at RT for 2 hours. The solvent was removed *in vacuo* to afford crude product (180 mg, 100%) as an oil. [M+H] MS Calcd.: $C_{16}H_{19}ClN_6O_2$, 363.1, Found: 363.1.

Step 6: (R)-N-(6-(3-((5-chloro-4-methoxypyrimidin-2-yl)amino)pyrrolidine-1-carbonyl)pyridin-3-yl)-N-methylacrylamide

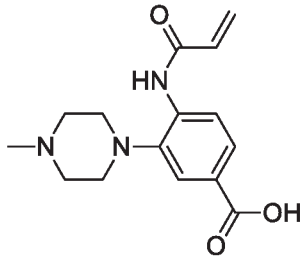


[00417] To a solution of (R)-(3-((5-chloro-4-methoxypyrimidin-2-yl)amino)pyrrolidin-1-yl)(5-(methylamino)pyridin-2-yl)methanone TFA salt (150 mg, 0.41 mmol) in DCM (5 mL) was added DIEA (210 mg, 1.64 mmol) at rt and the mixture was stirred at rt 30 minutes. Acryloyl chloride (75 mg, 0.82 mmol) was added dropwise, and the mixture was stirred at RT overnight. The solvent was removed *in vacuo* and the residue was purified by prep-HPLC to give the desired product (8 mg, 5%) as solid. [M+H] MS Calcd.: $C_{19}H_{21}ClN_6O_3$, 417.2, Found: 417.2.

Example 78: Synthesis of (R)-N-(4-(3-((5-chloro-4-methoxypyrimidin-2-yl)amino)pyrrolidine-1-carbonyl)-2-(4-methylpiperazin-1-yl)phenyl)acrylamide

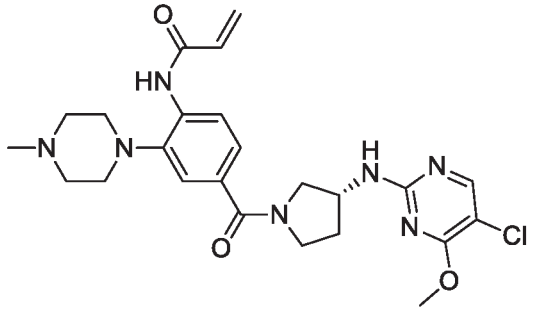


Step1: 4-acrylamido-3-(4-methylpiperazin-1-yl)benzoic acid



[00418] A mixture of 4-amino-3-(4-methylpiperazin-1-yl)benzoic acid (1.3 g, 5.5 mmol) in DMF (20 mL) was added Pyridine (1.3 g, 16.5 mmol) followed by acryloyl chloride (1.25 g, 13.8 mmol) at 0°C. The mixture was stirred at RT overnight. The mixture was concentrated and purified by column chromatography to afford 4-acrylamido-3-(piperidin-1-yl)benzoic acid (650 mg, 40%) as a brown solid. [M+H] Calc'd for $C_{15}H_{20}N_3O_3$, 290.1; Found, 290.1

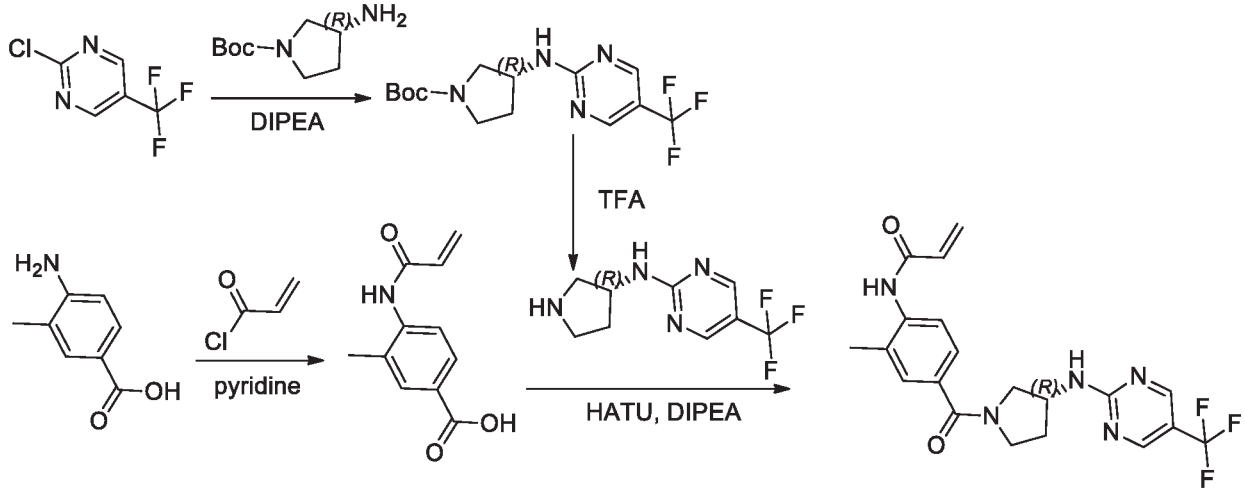
Step 2: (R)-N-(4-(3-((5-chloro-4-methoxypyrimidin-2-yl)amino)pyrrolidine-1-carbonyl)-2-(4-methylpiperazin-1-yl)phenyl)acrylamide



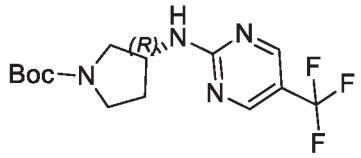
[00419] A mixture of 4-acrylamido-3-(piperidin-1-yl)benzoic acid (150 mg, 0.52 mmol), (R)-5-chloro-4-methoxy-N-(pyrrolidin-3-yl)pyrimidin-2-amine (HCl salt) (206 mg, 0.78 mmol), HATU (237 mg, 0.62 mmol) and DIEA (202 mg, 1.56 mmol) in DMF (10 mL) was stirred at RT overnight. The mixture was diluted with water (10 mL) and extracted with DCM (10 mL*3). The combined organic layer was washed with brine (20 mL), dried over Na_2SO_4, filtered and concentrated in-vacuo. The residue was purified by *prep*-HPLC to afford (R)-N-(4-(3-((5-chloro-4-methoxypyrimidin-2-yl)amino)pyrrolidine-1-carbonyl)-2-(4-methylpiperazin-1-yl)phenyl)acrylamide (16.3 mg, 6.3%) as a white solid (TFA salt). ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.88-2.00 (m, 1H), 2.09-2.20 (m, 1H), 2.25 (s, 3H), 2.50-2.54 (m, 4H), 2.79-2.84 (m, 4H), 3.40-3.94 (m, 7H), 4.24-4.43 (m, 1H), 5.78 (d, J = 10.4 Hz, 1H), 6.23 (s, 0.5H), 6.28 (s, 0.5H), 6.60-6.67

(m, 1H), 7.22-7.32 (m, 2H), 7.68 (br s, 1H), 8.00-8.14 (m, 2H), 9.08 (s, 0.5H), 9.10 (s, 0.5H). [M+H] Calc'd for $C_{24}H_{31}ClN_7O_3$, 500.2; Found, 500.2.

Example 79: Synthesis of (*R*)-*N*-(2-methyl-4-(3-((5-(trifluoromethyl)pyrimidin-2-yl)amino)pyrrolidine-1-carbonyl)phenyl)acrylamide

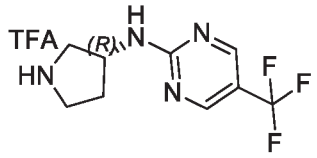


Step 1: (R)-tert-butyl 3-((5-(trifluoromethyl)pyrimidin-2-yl)amino)pyrrolidine-1-carboxylate



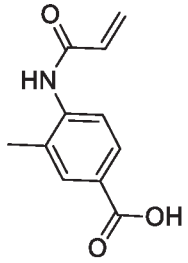
[00420] The title compound was prepared in 96% yield from 2-chloro-5-(trifluoromethyl)pyrimidine using general procedure of (*R*)-*tert*-butyl 3-((5-chloro-4-methylpyrimidin-2-yl)amino)pyrrolidine-1-carboxylate. [M+H] Calc'd for $C_{14}H_{19}F_3N_4O_2$, 333.1; Found, 333.1.

Step 2: (R)-N-(pyrrolidin-3-yl)-5-(trifluoromethyl)pyrimidin-2-amine 2,2,2-trifluoroacetate



[00421] The title compound was prepared in 100% yield from (*R*)-*tert*-butyl 3-((5-(trifluoromethyl)pyrimidin-2-yl)amino)pyrrolidine-1-carboxylate using general procedure of (*R*)-5-chloro-4-methyl-N-(pyrrolidin-3-yl)pyrimidin-2-amine 2,2,2-trifluoroacetate. [M+H] Calc'd for $C_9H_{11}F_3N_4$, 233.0; Found, 233.0.

Step 3: 4-acrylamido-3-methylbenzoic acid

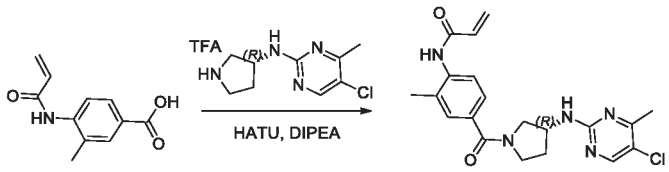


[00422] To a solution of 4-amino-3-methylbenzoic acid (13.7 g, 91.0 mmol) and pyridine (5 mL) in DMF (100 mL) was added acryloyl chloride (12.4 g, 136.5 mmol) at 0°C. The mixture was stiired at RT for 4 hours. The mixture was diluted with water (1000 mL) and filtered. The filter cake was washed with water (200 mL*2) and dried to afford 4-acrylamido-3-methylbenzoic acid (15.1 g, 81%) as a white solid. [M+H] Calc'd for $C_{11}H_{11}NO_3$, 206.0; Found, 206.0.

Step 4: (R)-N-(2-methyl-4-(3-((5-(trifluoromethyl)pyrimidin-2-yl)amino)pyrrolidine-1-carbonyl)phenyl)acrylamide

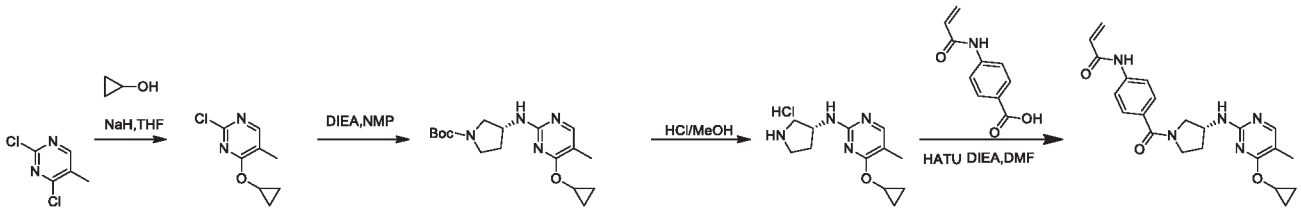
[00423] The title compound was prepared in 20% yield from 4-acrylamido-3-methylbenzoic acid using general procedure of (*R*)-*N*-(4-(3-((5-chloro-4-methylpyrimidin-2-yl)amino)pyrrolidine-1-carbonyl)phenyl)acrylamide. ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.90-2.07 (m, 1H), 2.16-2.27 (m, 4H), 3.38-3.72 (m, 3H), 3.78-3.82 (m, 1H), 4.35-4.55 (m, 1H), 5.78 (d, *J* = 10.0 Hz, 1H), 6.27 (d, *J* = 17.2 Hz, 1H), 6.54-6.61 (m, 1H), 7.32-7.42 (m, 2H), 7.61-7.66 (m, 1H), 8.41-8.44 (m, 1H), 8.63-8.71 (m, 2H), 9.51 (s, 0.5H), 9.54 (s, 0.5H). [M+H] Calc'd for $C_{20}H_{20}F_3N_5O_2$, 420.1; Found, 420.1.

Example 80: Synthesis of (*R*)-*N*-(4-(3-((5-chloro-4-methylpyrimidin-2-yl)amino)pyrrolidine-1-carbonyl)-2-methylphenyl)acrylamide

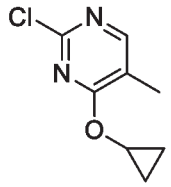


[00424] The title compound was prepared in 16% yield from 4-acrylamido-3-methylbenzoic acid using general procedure of (*R*)-*N*-(4-(3-((5-chloro-4-methylpyrimidin-2-yl)amino)pyrrolidine-1-carbonyl)phenyl)acrylamide. ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.84-1.99 (m, 1H), 2.00-2.36 (m, 7H), 3.48-3.55 (m, 2H), 3.59-3.68 (m, 1H), 3.72-3.76 (m, 1H), 4.25-4.42 (m, 1H), 5.78 (d, *J* = 10.4 Hz, 1H), 6.26 (d, *J* = 16.8 Hz, 1H), 6.53-6.60 (m, 1H), 7.30-7.40 (m, 2H), 7.61 (t, *J* = 8.8 Hz, 1H), 7.70 (s, 1H), 8.19 (s, 0.5H), 8.26 (s, 0.5H), 9.52 (d, *J* = 8.0 Hz, 1H). [M+H] Calc'd for $C_{20}H_{22}ClN_5O_2$, 400.1; Found, 400.1.

Example 81: Synthesis of (*R*)-*N*-(4-(3-((4-cyclopropoxy-5-methylpyrimidin-2-yl)amino)pyrrolidine-1-carbonyl)phenyl)acrylamide

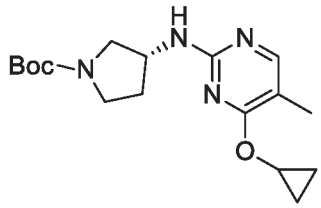


Step 1: 2-chloro-4-cyclopropoxy-5-methylpyrimidine



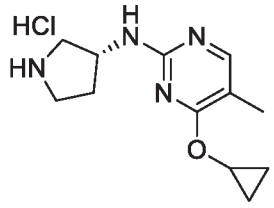
[00425] To a solution of cyclopropanol (1.2 g, 20.1 mmol) in THF (30 mL) was added NaH (960 mg, 24.0 mmol, 60% wt in mineral oil) at 0°C. The mixture was stirred at 0°C under N_2 for 30 minutes. Then 2,4-dichloro-5-methylpyrimidine (3.2 g, 19.6 mmol) was added. The mixture was stirred at 0°C to RT under N_2 for 6 hours. The mixture diluted with water (100 mL) and extracted with EtOAc (100 mL*2). The combined organic phase was washed with brine (100 mL), dried over Na_2SO_4, filtered and concentrated *in vacuo* to afford 2-chloro-4-cyclopropoxy-5-methylpyrimidine (3.0 g, 81%) as a yellow solid. [M+H] Calc'd for $C_8H_9ClN_2O$, 185.0; Found, 185.0.

Step 2: (R)-tert-butyl 3-((4-cyclopropoxy-5-methylpyrimidin-2-yl)amino)pyrrolidine-1-carboxylate



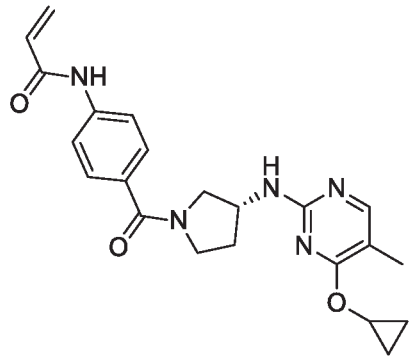
[00426] The title compound was prepared in 58% yield from 2-chloro-4-cyclopropoxy-5-methylpyrimidine using general procedure of (*R*)-*tert*-butyl 3-((5-chloro-4-methylpyrimidin-2-yl)amino)pyrrolidine-1-carboxylate. [M+H] Calc'd for $C_{17}H_{26}N_4O_3$, 335.2; Found, 335.2.

Step 3: (R)-4-cyclopropoxy-5-methyl-N-(pyrrolidin-3-yl)pyrimidin-2-amine hydrochloride



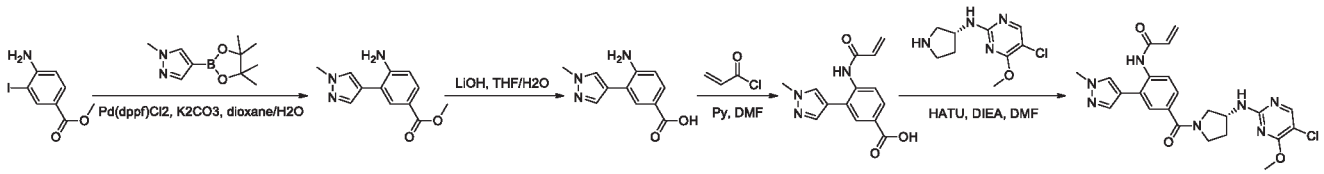
[00427] The title compound was prepared in 100% yield from (*R*)-*tert*-butyl 3-((4-cyclopropoxy-5-methylpyrimidin-2-yl)amino)pyrrolidine-1-carboxylate using general procedure of (*R*)-5-chloro-4-cyclopropoxy-*N*-(pyrrolidin-3-yl)pyrimidin-2-amine hydrochloride. [M+H] Calc'd for $C_{12}H_{18}N_4O$, 235.1; Found, 235.1.

Step 4: (R)-N-(4-(3-((4-cyclopropoxy-5-methylpyrimidin-2-yl)amino)pyrrolidine-1-carbonyl)phenyl)acrylamide

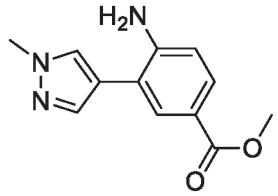


[00428] The title compound was prepared in 21% yield from (*R*)-4-cyclopropoxy-5-methyl-*N*-(pyrrolidin-3-yl)pyrimidin-2-amine hydrochloride using general procedure of (*R*)-*N*-(4-(3-((5-chloro-4-methylpyrimidin-2-yl)amino)pyrrolidine-1-carbonyl)phenyl)acrylamide. ^{1}H NMR (400 MHz, DMSO-d_6): δ 0.52-0.78 (m, 4H), 1.80 (s, 1.5H), 1.86 (s, 1.5H), 1.90-2.15 (m, 2H), 3.36-3.86 (m, 4H), 4.14-4.31 (m, 2H), 5.78 (d, J = 10.4 Hz, 1H), 6.28 (d, J = 16.8 Hz, 1H), 6.41-6.47 (m, 1H), 7.17 (s, 1H), 7.48-7.53 (m, 2H), 7.68-7.72 (m, 2H), 7.80 (s, 0.5H), 7.88 (s, 0.5H), 10.29 (s, 1H). [M+H] Calc'd for $C_{22}H_{25}N_5O_3$, 408.1; Found, 408.1.

Example 82: Synthesis of (R)-N-(4-(3-((5-chloro-4-methoxypyrimidin-2-yl)amino)pyrrolidine-1-carbonyl)-2-(1-methyl-1H-pyrazol-4-yl)phenyl)acrylamide

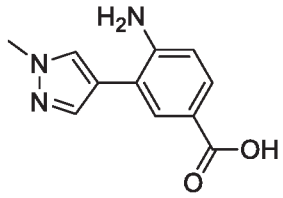


Step 1: methyl 4-amino-3-(1-methyl-1H-pyrazol-4-yl)benzoate



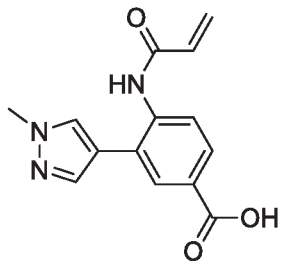
[00429] A mixture of methyl 4-amino-3-iodobenzoate (500 mg, 1.81 mmol), 1-methyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1H-pyrazole (563 mg, 2.71 mmol), $Pd(dppf)Cl_2$ (132 mg, 0.18 mmol) and Cs_2CO_3 (1177 mg, 3.61 mmol) in dioxane/ H_2O (10 mL/2 mL) was stirred at 90°C for 8h. The mixture was diluted with water (30 mL) and extracted with DCM (10 mL* 3). The combined organic layer was washed with brine (50 mL), dried over Na_2SO_4, filtered and concentrated *in vacuo*. The residue was purified by column (PE:EA = 1:1) to afford methyl 4-amino-3-(1-methyl-1H-pyrazol-4-yl)benzoate (400 mg, 96%) as brown solid. [M+H] Calc'd for $C_{12}H_{13}N_3O_2$, 232.1; Found, 232.1.

Step 2: 4-amino-3-(1-methyl-1H-pyrazol-4-yl)benzoic acid



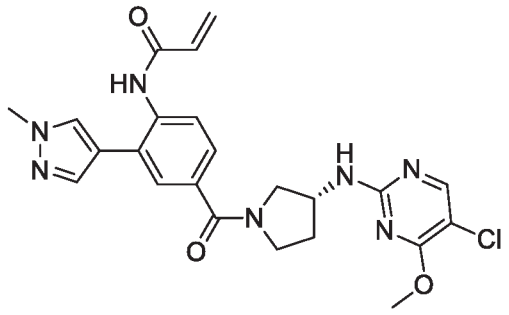
[00430] A mixture of methyl 4-amino-3-(1-methyl-1H-pyrazol-4-yl)benzoate (400 mg, 1.81 mmol) and LiOH (235 mg, 5.60 mmol) in THF/H_2O (20 mL/10 mL) was stirred at 40°C for 24 h. The mixture was then adjusted to pH=3 and extracted with DCM (10 mL* 3). The combined organic layer was washed with brine (50 mL), dried over Na_2SO_4, filtered and concentrated *in vacuo* to afford 4-amino-3-(1-methyl-1H-pyrazol-4-yl)benzoic acid (300 mg, 76%) as brown solid. [M+H] Calc'd for $C_{11}H_{11}N_3O_2$, 218.0; Found, 218.0.

Step 3: 4-acrylamido-3-(1-methyl-1H-pyrazol-4-yl)benzoic acid



[00431] A mixture of 4-amino-3-(1-methyl-1H-pyrazol-4-yl)benzoic acid (300 mg, 1.38 mmol) in DMF (15 mL) was added Pyridine (328 mg) at 0°C followed by acryloyl chloride (188 mg, 2.08 mmol). The mixture was then stirred at RT for 5h. The mixture was concentrated and added DCM (20 mL), washed with 0.5N HCl (5 mL), dried over Na_2SO_4, filtered, concentrated *in vacuo* to afford 4-acrylamido-3-(1-methyl-1H-pyrazol-4-yl)benzoic acid (150 mg, 40%) as brown solid. [M+H] Calc'd for $C_{14}H_{13}N_3O_3$, 272.1; Found, 272.1

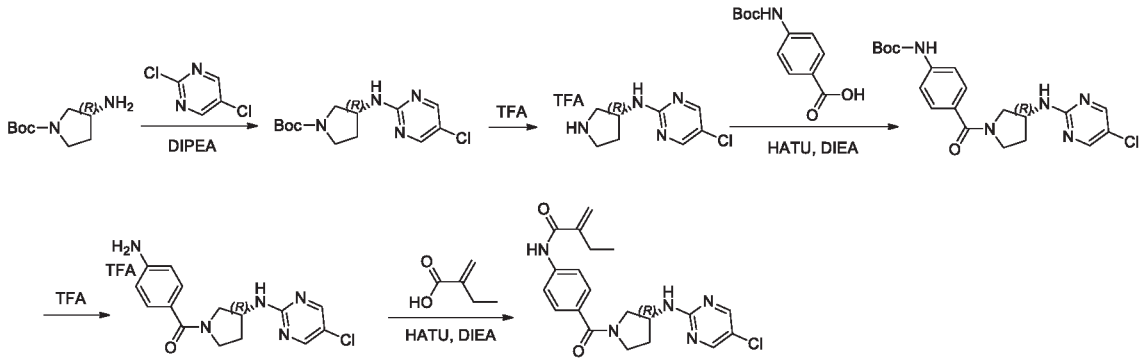
Step 4: (R)-N-(4-(3-((5-chloro-4-methoxypyrimidin-2-yl)amino)pyrrolidine-1-carbonyl)-2-(1-methyl-1H-pyrazol-4-yl)phenyl)acrylamide



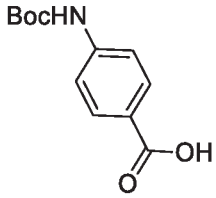
[00432] A mixture of 4-acrylamido-3-(1-methyl-1H-pyrazol-4-yl)benzoic acid (150 mg, 0.55 mmol), (R)-5-chloro-4-methoxy-N-(pyrrolidin-3-yl)pyrimidin-2-amine (HCl salt) (175 mg, 0.66 mmol), HATU (252 mg, 0.66 mmol), DIEA (286 mg, 2.22 mmol) in DMF (10 mL) was stirred at RT for

overnight. The mixture was diluted with water (50 mL) and extracted with DCM (50 mL* 3). The combined organic layer was washed with brine (20 mL), dried over Na_2SO_4, filtered and concentrated in-vacuo. The residue was then purified by *prep*-HPLC to afford (R)-N-(4-(3-((5-chloro-4-methoxypyrimidin-2-yl)amino)pyrrolidine-1-carbonyl)-2-(1-methyl-1H-pyrazol-4-yl)phenyl)acrylamide (48.2 mg, 18%) as a white solid (TFA salt). ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.90-2.03 (m, 1H), 2.14-2.17 (m, 1H), 3.39-3.70 (m, 3H), 3.79-3.95 (m, 7H), 4.24-4.45 (m, 1H), 5.75 (d, J = 10.4 Hz, 1H), 6.23 (s, 0.5H), 6.27 (s, 0.5H), 6.48-6.56 (m, 1H), 7.36-7.41 (m, 1H), 7.56-7.73 (m, 4H), 7.97 (s, 0.5H), 7.99 (s, 0.5H), 8.08-8.16 (m, 1H), 9.62 (s, 1H). [M+H] Calc'd for $C_{23}H_{24}ClN_7O_3$, 482.0; Found, 482.0.

Example 83: Synthesis of (*R*)-*N*-(4-(3-((5-chloropyrimidin-2-yl)amino)pyrrolidine-1-carbonyl)phenyl)-2-methylenebutanamide

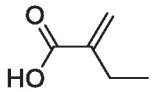


Step 1: 4-((tert-butoxycarbonyl)amino)benzoic acid



[00433] To a solution of 4-aminobenzoic acid (5.0 g, 36.5 mmol) and TEA (7.4 g, 73 mmol) in dioxane (45 mL) and H_2O (20 mL) was added di-tert-butyl dicarbonate (15.9 g, 73 mmol) at RT. The solution was stirred at RT for overnight. The solution was concentrated to afford 4-((tert-butoxycarbonyl)amino)benzoic acid (7.0 g, 81%) as a white solid. [M+H] Calc'd for $C_{12}H_{15}NO_4$, 238.1; Found, 238.1.

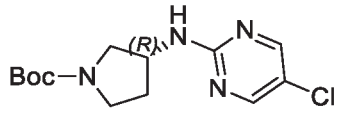
Step 2: 2-methylenebutanoic acid



[00434] To a solution of 2-ethylmalonic acid (1.5 g, 11.4 mmol) in EtOAc (114 mL) was added Paraformaldehyde (680 mg, 22.7 mmol) and diethylamine (1.2 g, 17.0 mmol) at 0°C. The mixture was refluxed for 4 hours. The solution was cooled to R.T and concentrated. The residue was

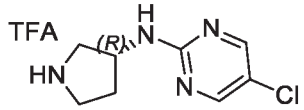
quenched with ice-water and acidified to pH 1.0 with con.HCl. The solution was extracted with DCM (100 mL*3). The combined organic phase was washed with brine (100 mL), dried over Na_2SO_4, filtered and concentrated *in vacuo*. The residue was purified by flash chromatography on silica gel (petroleum ether/EtOAc = 1/1) to afford 2-methylenebutanoic acid (700 mg, 64%) as colorless oil. [M+H] Calc'd for $C_5H_8O_2$, 101.0; Found, 101.0.

Step 3: (R)-tert-butyl 3-((5-chloropyrimidin-2-yl)amino)pyrrolidine-1-carboxylate



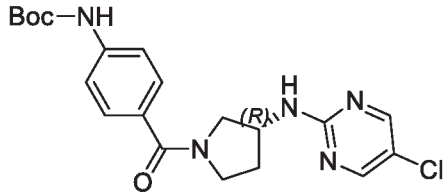
[00435] The title compound was prepared in 82% yield from 2,5-dichloropyrimidine using general procedure of (*R*)-*tert*-butyl 3-((5-chloro-4-methylpyrimidin-2-yl)amino)pyrrolidine-1-carboxylate. [M+H] Calc'd for $C_{13}H_{19}ClN_4O_2$, 299.1; Found, 299.1.

Step 4: (R)-5-chloro-N-(pyrrolidin-3-yl)pyrimidin-2-amine 2,2,2-trifluoroacetate



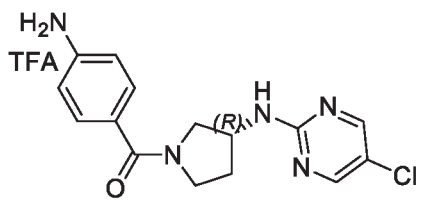
[00436] The title compound was prepared in 100% yield from (R)-tert-butyl 3-((5-chloropyrimidin-2-yl)amino)pyrrolidine-1-carboxylate using general procedure of (*R*)-5-chloro-4-methyl-N-(pyrrolidin-3-yl)pyrimidin-2-amine 2,2,2-trifluoroacetate. [M+H] Calc'd for $C_8H_{11}ClN_4$, 199.0; Found, 199.0.

Step 5: (R)-tert-butyl (4-(3-((5-chloropyrimidin-2-yl)amino)pyrrolidine-1-carbonyl)phenyl)carbamate



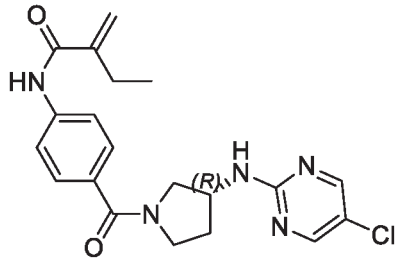
[00437] The title compound was prepared in 64% yield from 4-((*tert*-butoxycarbonyl)amino)benzoic acid using general procedure of (*R*)-*N*-(4-(3-((5-chloro-4-methylpyrimidin-2-yl)amino)pyrrolidine-1-carbonyl)phenyl)acrylamide. [M+H] Calc'd for $C_{20}H_{24}ClN_5O_3$, 418.1; Found, 418.1.

Step 6: (R)-(4-aminophenyl)(3-((5-chloropyrimidin-2-yl)amino)pyrrolidin-1-yl)methanone 2,2,2-trifluoroacetate



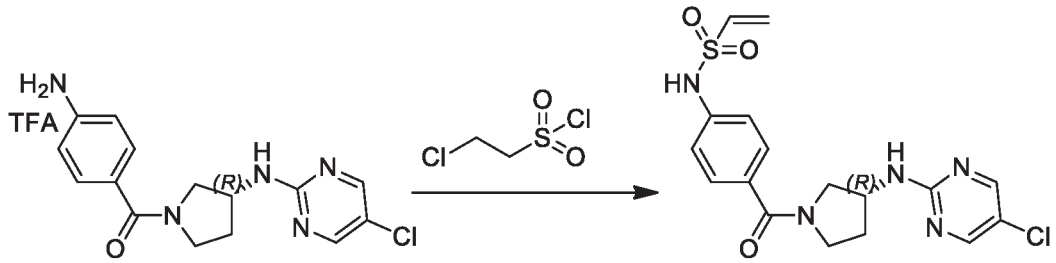
[00438] The title compound was prepared in 100% yield from (*R*)-*tert*-butyl (4-(3-((5-chloropyrimidin-2-yl)amino)pyrrolidine-1-carbonyl)phenyl)carbamate using general procedure of (*R*)-5-chloro-4-methyl-N-(pyrrolidin-3-yl)pyrimidin-2-amine 2,2,2-trifluoroacetate. [M+H] Calc'd for $C_{15}H_{16}ClN_5O$, 318.1; Found, 318.1.

Step 7: (R)-N-(4-(3-((5-chloropyrimidin-2-yl)amino)pyrrolidine-1-carbonyl)phenyl)-2-methylenebutanamide



[00439] The title compound was prepared in 32% yield from (*R*)-(4-aminophenyl)(3-((5-chloropyrimidin-2-yl)amino)pyrrolidin-1-yl)methanone 2,2,2-trifluoroacetate using general procedure of (*R*)-*N*-(4-(3-((5-chloro-4-methylpyrimidin-2-yl)amino)pyrrolidine-1-carbonyl)phenyl)acrylamide. ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.02 (t, *J* = 7.6 Hz, 3H), 1.87-2.01 (m, 1H), 2.07-2.18 (m, 1H), 2.32-2.36 (m, 2H), 3.40-3.54 (m, 2H), 3.63-3.80 (m, 2H), 4.21-4.40 (m, 1H), 5.47 (s, 1H), 5.76 (d, *J* = 4.0 Hz, 1H), 7.46-7.51 (m, 2H), 7.71-7.76 (m, 2H), 7.81-7.83 (m, 1H), 8.32 (s, 1H), 8.39 (s, 1H), 10.02 (s, 1H). [M+H] Calc'd for $C_{20}H_{22}ClN_5O_2$, 400.1; Found, 400.1.

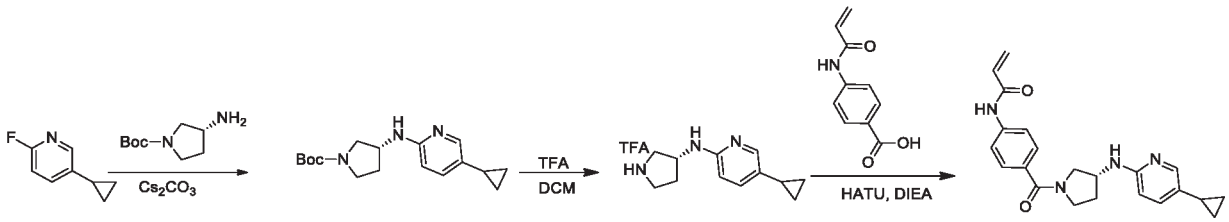
Example 84: Synthesis of (*R*)-*N*-(4-(3-((5-chloropyrimidin-2-yl)amino)pyrrolidine-1-carbonyl)phenyl)ethenesulfonamide



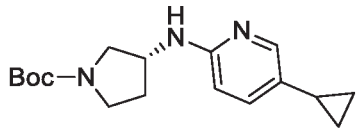
[00440] To a solution of (R)-(4-aminophenyl)(3-((5-chloropyrimidin-2-yl)amino)pyrrolidin-1-yl)methanone 2,2,2-trifluoroacetate (91 mg, 0.29 mmol) in DCM (1.5 mL) was added DIEA (176 mg, 1.74 mmol) and 2-chloroethanesulfonyl chloride (47 mg, 0.29 mmol) in DCM (0.5 mL) dropwise at 0°C. The solution was stirred at RT for 5 hours. The solution was concentrated and the residue was purified by *prep*-HPLC to afford (*R*)-*N*-(4-(3-((5-chloropyrimidin-2-yl)amino)pyrrolidine-1-carbonyl)phenyl)ethenesulfonamide (19.8 mg, 17%) as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.84-2.00 (m, 1H), 2.07-2.17 (m, 1H), 3.29-3.31 (m, 1H), 3.40-3.66 (m, 2H), 3.72-3.76 (m, 1H), 4.21-4.40 (m, 1H), 6.07 (dd, *J* = 2.8 Hz, 9.6 Hz, 1H), 6.17 (dd, *J* = 3.6 Hz, 16.4 Hz, 1H), 6.79-

6.86 (m, 1H), 7.13-7.18 (m, 2H), 7.45-7.50 (m, 2H), 7.81-7.84 (m, 1H), 8.32 (s, 1H), 8.38 (s, 1H), 10.21 (br s, 1H). [M+H] Calc'd for $C_{17}H_{18}ClN_5O_3S$, 408.0; Found, 408.0.

Example 85: Synthesis of (*R*)-*N*-(4-(3-((5-cyclopropylpyridin-2-yl)amino)pyrrolidine-1-carbonyl)phenyl)acrylamide

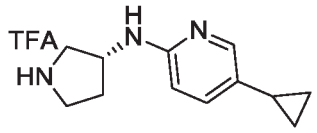


Step 1: (R)-tert-butyl 3-((5-cyclopropylpyridin-2-yl)amino)pyrrolidine-1-carboxylate



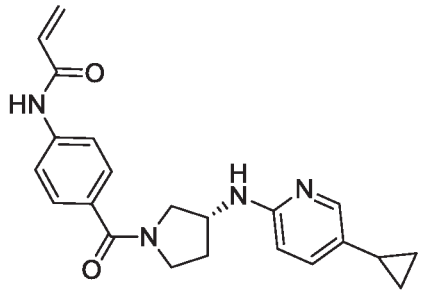
[00441] A mixture of 5-cyclopropyl-2-fluoropyridine (543 mg, 2.92 mmol), (R)-tert-butyl 3-aminopyrrolidine-1-carboxylate (400 mg, 2.92 mmol) and Cs_2CO_3 (1904 mg, 5.84 mmol) in DMSO (2 mL) was stirred at 160 °C for 24 hours. The mixture was cooled to RT diluted with water (20 mL) and extracted with EtOAc (20 mL*3). The combined organic phase was concentrated and the residue was purified by flash chromatography on silica gel (PE/EtOAc = 2/1) to afford (R)-tert-butyl 3-((5-cyclopropylpyridin-2-yl)amino)pyrrolidine-1-carboxylate (35 mg, 4%) as a yellow solid. [M+H] Calc'd for $C_{17}H_{25}N_3O_2$, 304.1; Found, 304.1.

Step 2: (R)-5-cyclopropyl-N-(pyrrolidin-3-yl)pyridin-2-amine 2,2,2-trifluoroacetate



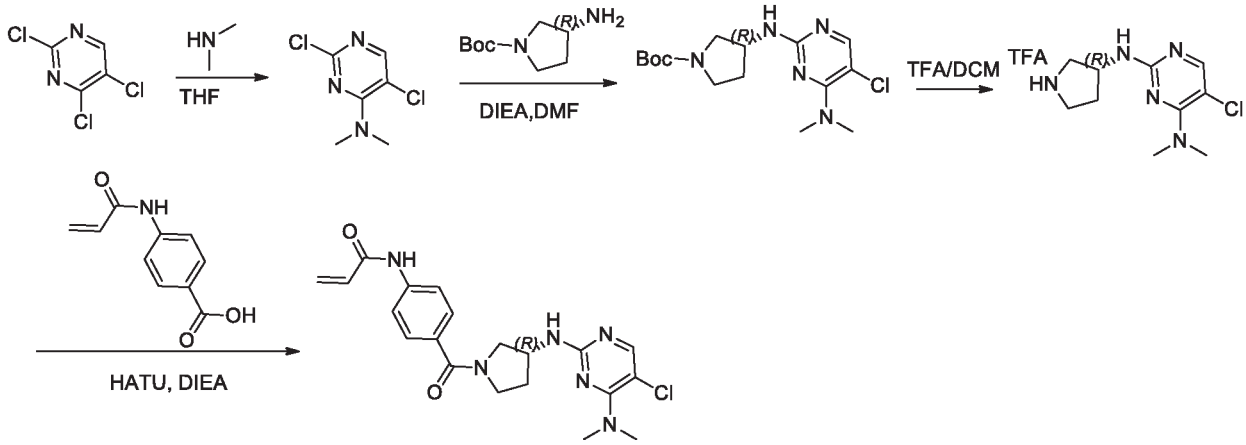
[00442] The title compound was prepared in 100% yield from (R)-tert-butyl 3-((5-cyclopropylpyridin-2-yl)amino)pyrrolidine-1-carboxylate using general procedure of (*R*)-5-chloro-4-methyl-N-(pyrrolidin-3-yl)pyrimidin-2-amine 2,2,2-trifluoroacetate. [M+H] Calc'd for $C_{12}H_{17}N_3$, 204.1; Found, 204.1.

Step 3: (R)-N-(4-(3-((5-cyclopropylpyridin-2-yl)amino)pyrrolidine-1-carbonyl)phenyl)acrylamide

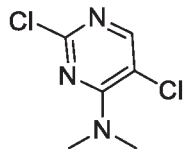


[00443] The title compound was prepared in 13% yield from (*R*)-5-cyclopropyl-N-(pyrrolidin-3-yl)pyridin-2-amine 2,2,2-trifluoroacetate using general procedure of (*R*)-*N*-(4-(3-((5-chloro-4-methylpyrimidin-2-yl)amino)pyrrolidine-1-carbonyl)phenyl)acrylamide. ^{1}H NMR (400 MHz, DMSO-d_6): δ 0.47-0.54 (m, 2H), 0.76-0.83 (m, 2H), 1.68-1.92 (m, 2H), 2.07-2.19 (m, 1H), 3.25-3.29 (m, 1H), 3.50-3.66 (m, 2H), 3.74-3.82 (m, 1H), 4.22-4.36 (m, 1H), 5.78 (d, *J* = 10.0 Hz, 1H), 6.25-6.29 (m, 1H), 6.37-6.47 (m, 2H), 6.56-6.60 (m, 1H), 7.03-7.10 (m, 1H), 7.49-7.54 (m, 1H), 7.68-7.85 (m, 3H), 10.32 (br s, 1H). [M+H] Calc'd for $C_{22}H_{24}N_4O_2$, 377.1; Found, 377.1.

Example 86: Synthesis of (*R*)-*N*-(4-(3-((5-chloro-4-(dimethylamino)pyrimidin-2-yl)amino)pyrrolidine-1-carbonyl)phenyl)acrylamide

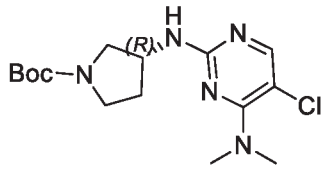


Step 1: 2,5-dichloro-N,N-dimethylpyrimidin-4-amine



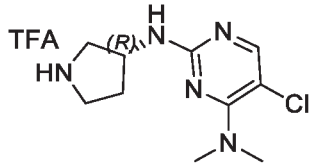
[00444] To a mixture of 2,4,5-trichloropyrimidine (400 mg, 2.19 mmol) in THF (4 mL) was added dimethylamine (295 mg, 6.56mmol) at 0°C. The mixture was stirred at 5°C for 2 hours. The mixture was diluted with water (10 mL) and extracted with EtOAc (50 mL*3). The combined organic phase was concentrated *in vacuo*. The residue was purified by reverse colum to afford 2,5-dichloro-*N*,*N*-dimethylpyrimidin-4-amine (196 mg, 47%) as colorless oil. [M+H] Calc'd for $C_6H_7Cl_2N_3$, 192.0; Found, 192.0.

Step 2: (R)-tert-butyl 3-((5-chloro-4-(dimethylamino)pyrimidin-2-yl)amino)pyrrolidine-1-carboxylate



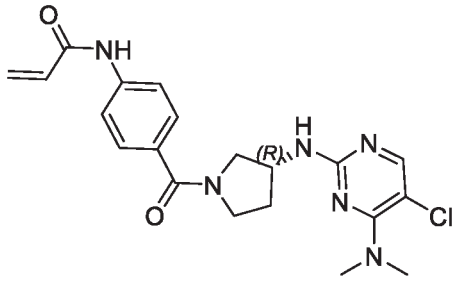
[00445] The title compound was prepared in 28% yield from 2,5-dichloro-*N*,*N*-dimethylpyrimidin-4-amine using general procedure of (*R*)-*tert*-butyl 3-((5-chloro-4-methylpyrimidin-2-yl)amino)pyrrolidine-1-carboxylate. [M+H] Calc'd for $C_{15}H_{24}ClN_5O_2$, 342.1; Found, 342.1.

Step 3: (R)-5-chloro-N4,N4-dimethyl-N2-(pyrrolidin-3-yl)pyrimidine-2,4-diamine 2,2,2-trifluoroacetate



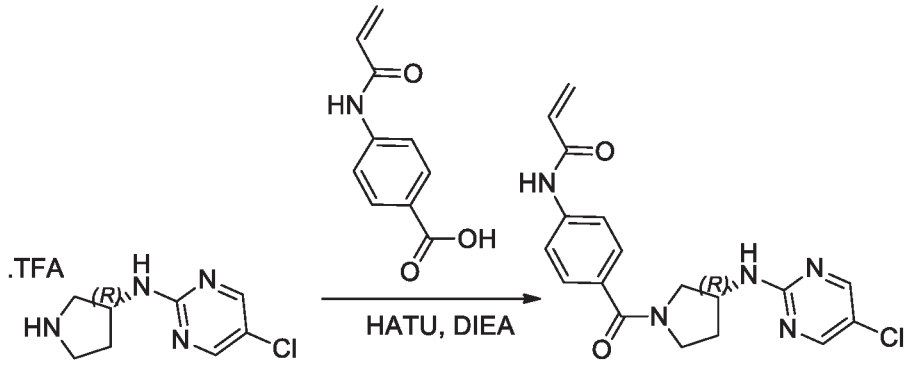
[00446] The title compound was prepared in 100% yield from (*R*)-*tert*-butyl 3-((5-chloro-4-(dimethylamino)pyrimidin-2-yl)amino)pyrrolidine-1-carboxylate using general procedure of (*R*)-5-chloro-4-methyl-N-(pyrrolidin-3-yl)pyrimidin-2-amine 2,2,2-trifluoroacetate. [M+H] Calc'd for $C_{10}H_{16}ClN_5$, 242.1; Found, 242.1.

Step 4: (R)-N-(4-(3-((5-chloro-4-(dimethylamino)pyrimidin-2-yl)amino)pyrrolidine-1-carbonyl)phenyl)acrylamide

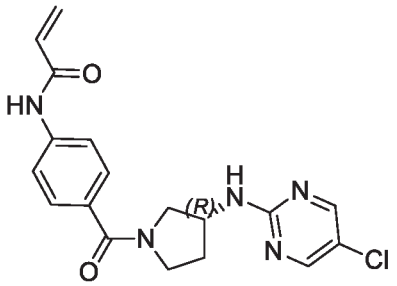


[00447] The title compound was prepared in 26% yield from (*R*)-5-chloro-N^4,N^4-dimethyl-N^2-(pyrrolidin-3-yl)pyrimidine-2,4-diamine 2,2,2-trifluoroacetate using general procedure of (*R*)-*N*-(4-(3-((5-chloro-4-methylpyrimidin-2-yl)amino)pyrrolidine-1-carbonyl)phenyl)acrylamide. ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.87-1.99 (m, 1H), 2.07-2.15 (m, 1H), 3.02 (s, 3H), 3.10 (s, 3H), 3.42-3.55 (m, 2H), 3.61-3.77 (m, 2H), 4.19-4.36 (m, 1H), 5.78 (d, J = 11.2 Hz, 1H), 6.28 (d, J = 16.8 Hz, 1H), 6.41-6.48 (m, 1H), 7.16 (br s, 1H), 7.48-7.53 (m, 2H), 7.69-7.73 (m, 2H), 7.80 (s, 0.5H), 7.86 (s, 0.5H), 10.30 (s, 1H). [M+H] Calc'd for $C_{20}H_{23}ClN_6O$, 415.1; Found, 415.1.

Example 87: Synthesis of (R)-N-(4-(3-((5-chloropyrimidin-2-yl)amino)pyrrolidine-1-carbonyl)phenyl)acrylamide

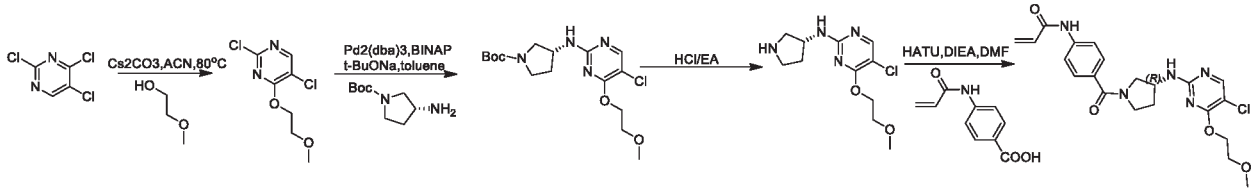


Step 1: (R)-N-(4-(3-((5-chloropyrimidin-2-yl)amino)pyrrolidine-1-carbonyl)phenyl)acrylamide

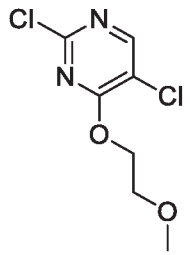


[00448] A mixture of (R)-5-chloro-N-(pyrrolidin-3-yl)pyrimidin-2-amine TFA salt (3.8 g, 10.4 mmol), 4-acrylamidobenzoic acid (2.0 g, 10.4 mmol), HATU (4.7 g, 12.5 mmol) and DIPEA (6.7 g, 52.0 mmol) in DMF (5.0 mL) was stirred at RT for 3 hours. The reaction mixture was diluted with H_2O (100 mL) and extracted with EtOAc (100 mL*2). The combined organics were washed with brine (100 mL), dried over Na_2SO_4, filtered and concentrated. The residue was purified by *prep*-HPLC to give (R)-N-(4-(3-((5-chloropyrimidin-2-yl)amino)pyrrolidine-1-carbonyl)phenyl)acrylamide (1.8 g, 47%). ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.86-2.02 (m, 1H), 2.07-2.19 (m, 1H), 3.30-3.37 (m, 1H), 3.40-3.48 (m, 1H), 3.51-3.62 (m, 1H), 3.70-3.80 (m, 1H), 4.24-4.26 (m, 0.5H), 4.39-4.41 (m, 0.5H), 5.78 (d, J = 10.8 Hz, 1H), 6.28 (d, J = 16.8 Hz, 1H), 6.41-6.50 (m, 1H), 7.28-7.31 (m, 2H), 7.48-7.54 (m, 2H), 7.81 (brs, 1H), 8.32 (s, 1H), 8.38 (s, 1H), 10.27 (brs, 1H). [M+H] MS Calcd.: $C_{19}H_{21}ClN_6O_3$, 372.1, Found: 372.1.

Example 88: Synthesis of (R)-N-(4-(3-((5-chloro-4-(2-methoxyethoxy)pyrimidin-2-yl)amino)pyrrolidine-1-carbonyl)phenyl)acrylamide

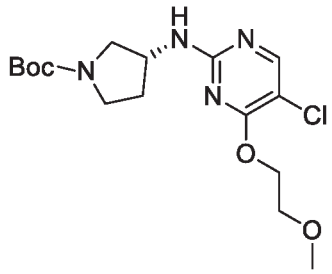


Step 1: 2,5-dichloro-4-(2-methoxyethoxy)pyrimidine



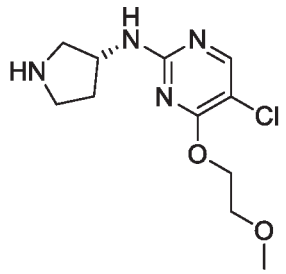
[00449] A mixture of 2,4,5-trichloropyrimidine (2.0 g, 10.9 mmol), 2-methoxyethanol (748 mg, 9.8 mmol), Cs_2CO_3 (5.3 g, 16.3 mmol) in CH_3CN (30 mL) was stirred at 80°C for 4h. The reaction mixture was cooled, added H_2O (40 mL) and extracted with EA (40 mL*2). The combined organic layer was dried over Na_2SO_4, concentrated and purified by silica gel chromatography (PE/EA = PE ~ 1/10) to afford 2,5-dichloro-4-(2-methoxyethoxy)pyrimidine (1.2 g, 50%) as colorless oil. [M+H] Calc'd for $C_7H_8Cl_2N_2O_2$, 222.9; Found, 222.9

Step 2: (R)-tert-butyl 3-((5-chloro-4-(2-methoxyethoxy)pyrimidin-2-yl)amino)pyrrolidine-1-carboxylate



[00450] A mixture of 2,5-dichloro-4-(2-methoxyethoxy)pyrimidine (1.2 g, 2.7 mmol), (R)-tert-butyl 3-aminopyrrolidine-1-carboxylate (1.1 g, 2.9 mmol), BINAP (1.3 g, 1.1 mmol), t-BuONa (778 mg, 4.1 mmol) and $Pd_2(dba)_3$ (622 mg, 5.4 mmol) in toluene (25 mL) was stirred at 100°C overnight. The reaction mixture was cooled, filtered and concentrated. The residue was purified by silica gel chromatography (PE/EA = 1/10 ~ 1/3) to afford (R)-tert-butyl 3-((5-chloro-4-(2-methoxyethoxy)pyrimidin-2-yl)amino)pyrrolidine-1-carboxylate (600 mg, 30%) as yellow oil. [M+H] Calc'd for $C_{16}H_{25}ClN_4O_4$, 373.1; Found, 373.1.

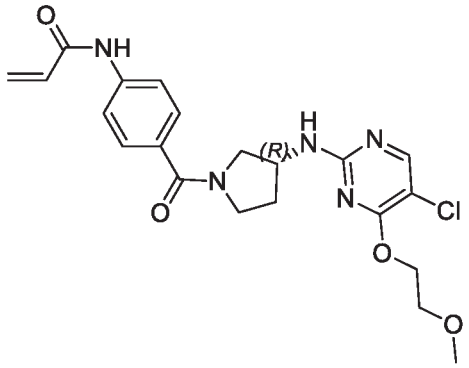
Step 3: (R)-5-chloro-4-(2-methoxyethoxy)-N-(pyrrolidin-3-yl)pyrimidin-2-amine



[00451] A mixture of (R)-tert-butyl 3-((5-chloro-4-(2-methoxyethoxy)pyrimidin-2-yl)amino)pyrrolidine-1-carboxylate (600 mg, 1.6 mmol) in HCl/EA (15 mL) was stirred at RT for 1h. The reaction mixture

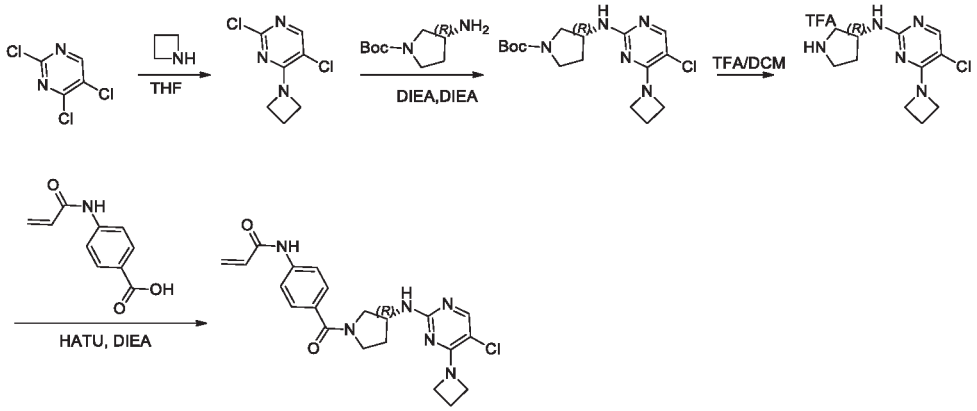
was concentrated to afford (R)-5-chloro-4-(2-methoxyethoxy)-N-(pyrrolidin-3-yl)pyrimidin-2-amine (400 mg, 91%) as yellow oil. [M+H] Calc'd for $C_{11}H_{17}ClN_4O_2$, 273.1; Found, 273.1.

Step 4: (R)-N-(4-(3-((5-chloro-4-(2-methoxyethoxy)pyrimidin-2-yl)amino)pyrrolidine-1-carbonyl)phenyl)acrylamide

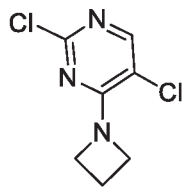


[00452] A mixture of (R)-5-chloro-4-(2-methoxyethoxy)-N-(pyrrolidin-3-yl)pyrimidin-2-amine (231 mg, 1.2 mmol), 4-acrylamidobenzoic acid (300 mg, 1.1 mmol), HATU (419 mg, 1.1 mmol) and DIEA (284 mg, 1.2 mmol) in DMF (15 mL) was stirred at RT for overnight. The reaction mixture was added H_2O (40 mL) and extracted with EA (40 mL*3). The combined organic layer was dried over Na_2SO_4, filtered and concentrated. The residue was purified by *prep*-HPLC to afford (R)-N-(4-(3-((5-chloro-4-(2-methoxyethoxy)pyrimidin-2-yl)amino)pyrrolidine-1-carbonyl)phenyl)acrylamide (219.2 mg, 45%) as a yellow solid. ^{1}H NMR (400 MHz, DMSO-d_6): 1.89-2.15 (m, 2H), 3.23 (s, 1H), 3.31 (s, 2H), 3.52-3.77 (m, 6H), 4.21-4.48 (m, 3H), 5.77-5.79 (d, J = 10.0 Hz, 1H), 6.25-6.30 (d, J = 17.2 Hz, 1H), 6.40-6.48 (m, 1H), 7.49-7.54 (m, 2H), 7.69-7.73 (m, 2H), 8.08-8.15 (m, 1H), 10.32-10.33 (d, J = 4.8 Hz, 1H). [M+H] Calc'd for $C_{21}H_{24}ClN_5O_4$, 446.1; Found, 446.1.

Example 89: Synthesis of (*R*)-*N*-(4-(3-((4-(azetidin-1-yl)-5-chloropyrimidin-2-yl)amino)pyrrolidine-1-carbonyl)phenyl)acrylamide

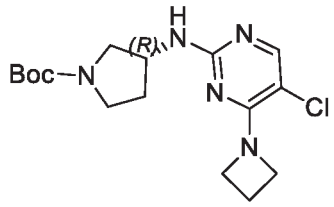


Step 1: 4-(azetidin-1-yl)-2,5-dichloropyrimidine



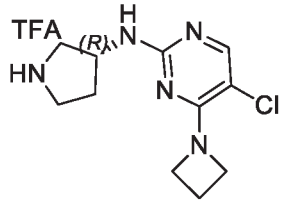
[00453] The title compound was prepared in 84% yield from 2,4,5-trichloropyrimidine using general procedure of 2,5-dichloro-*N*,*N*-dimethylpyrimidin-4-amine. [M+H] Calc'd for $C_7H_7Cl_2N_3$, 204.0; Found, 204.0.

Step 2: (R)-tert-butyl 3-((4-(azetidin-1-yl)-5-chloropyrimidin-2-yl)amino)pyrrolidine-1-carboxylate



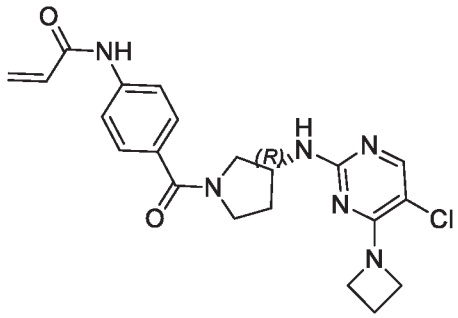
[00454] The title compound was prepared in 25% yield from 4-(azetidin-1-yl)-2,5-dichloropyrimidine using general procedure of (*R*)-*tert*-butyl 3-((5-chloro-4-methylpyrimidin-2-yl)amino)pyrrolidine-1-carboxylate. [M+H] Calc'd for $C_{16}H_{24}ClN_5O_2$, 354.1; Found, 354.1.

Step 3: (R)-4-(azetidin-1-yl)-5-chloro-N-(pyrrolidin-3-yl)pyrimidin-2-amine 2,2,2-trifluoroacetate



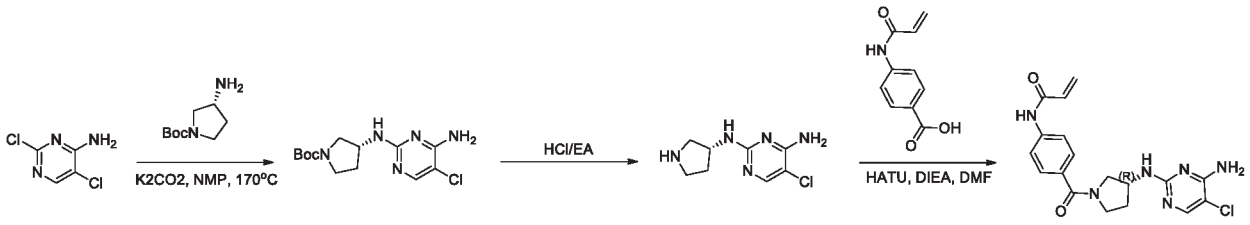
[00455] The title compound was prepared in 100% yield from (*R*)-*tert*-butyl 3-((4-(azetidin-1-yl)-5-chloropyrimidin-2-yl)amino)pyrrolidine-1-carboxylate using general procedure of (*R*)-5-chloro-4-methyl-N-(pyrrolidin-3-yl)pyrimidin-2-amine 2,2,2-trifluoroacetate. [M+H] Calc'd for $C_{11}H_{16}ClN_5$, 254.1; Found, 254.1.

Step 4: (*R*)-*N*-(4-(3-((4-(azetidin-1-yl)-5-chloropyrimidin-2-yl)amino)pyrrolidine-1-carbonyl)phenyl)acrylamide

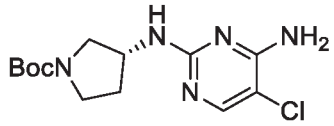


[00456] The title compound was prepared in 15% yield from (*R*)-4-(azetidin-1-yl)-5-chloro-N-(pyrrolidin-3-yl)pyrimidin-2-amine 2,2,2-trifluoroacetate using general procedure of (*R*)-*N*-(4-(3-((5-chloro-4-methylpyrimidin-2-yl)amino)pyrrolidine-1-carbonyl)phenyl)acrylamide. ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.83-2.05 (m, 1H), 2.07-2.11 (m, 1H), 2.18-2.33 (m, 2H), 3.27-3.32 (m, 1H), 3.47-3.77 (m, 3H), 4.14-4.34 (m, 5H), 5.77-5.80 (m, 1H), 6.25-6.30 (m, 1H), 6.41-6.48 (m, 1H), 7.14 (br s, 1H), 7.47-7.53 (m, 2H), 7.69-7.78 (m, 3H), 10.32 (s, 1H). [M+H] Calc'd for $C_{21}H_{23}ClN_6O_2$, 427.1; Found, 427.1.

Example 90: Synthesis of (R)-N-(4-(3-((4-amino-5-chloropyrimidin-2-yl)amino)pyrrolidine-1-carbonyl)phenyl)acrylamide

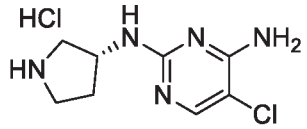


Step 1: (R)-tert-butyl 3-((4-amino-5-chloropyrimidin-2-yl)amino)pyrrolidine-1-carboxylate



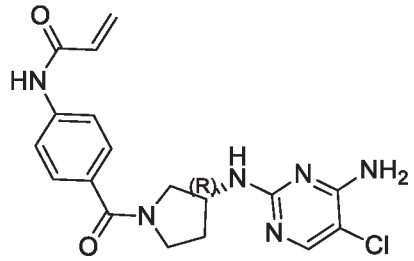
[00457] A mixture of 2,5-dichloropyrimidin-4-amine (500 mg, 3.0 mmol) and (R)-tert-butyl 3-aminopyrrolidine-1-carboxylate (1.1 g, 6.0 mmol) in NMP (20 mL) was added K_2CO_3 (830 mg, 6.0 mmol) at RT. The mixture was stirred at 170°C for 1.5h in microwave. The mixture was cooled, diluted with water (10 mL) and extracted with DCM (10 mL* 3). The combined organic layer was washed with brine (20 mL), dried over Na_2SO_4, filtered and concentrated *in vacuo*. The residue was purified by column (PE:EA = 1:1) to afford (R)-tert-butyl 3-((4-amino-5-chloropyrimidin-2-yl)amino)pyrrolidine-1-carboxylate (676 mg, 60%) as a yellow solid. [M+H] Calc'd for $C_{13}H_{21}ClN_5O_2$, 314.1; Found, 314.1

Step 2: (R)-5-chloro-N2-(pyrrolidin-3-yl)pyrimidine-2,4-diamine



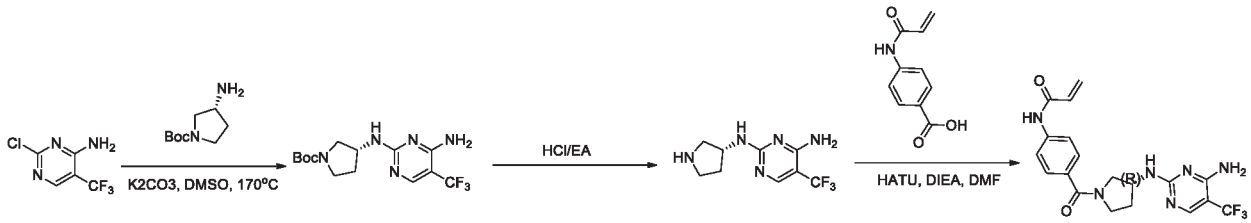
[00458] A mixture of (R)-tert-butyl 3-((4-amino-5-chloropyrimidin-2-yl)amino)pyrrolidine-1-carboxylate (576 mg, 1.84 mmol) in HCl/EA (10 mL) was stirred at RT for 3h. The reaction mixture was concentrated to afford (R)-5-chloro-N2-(pyrrolidin-3-yl)pyrimidine-2,4-diamine (600 mg, crude) as a yellow solid. [M+H] Calc'd for $C_8H_{13}ClN_5$, 214.0; Found, 214.0

Step 3: (R)-N-(4-(3-((4-amino-5-chloropyrimidin-2-yl)amino)pyrrolidine-1-carbonyl)phenyl)acrylamide

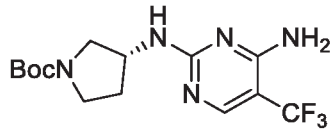


[00459] A mixture of 4-acrylamidobenzoic acid (150 mg, 0.78 mmol), (R)-5-chloro-N2-(pyrrolidin-3-yl)pyrimidine-2,4-diamine (HCl salt) (582 mg, 0.78 mmol), HATU (356 mg, 0.94 mmol) and DIEA (503 mg, 3.9 mmol) in DMF (15 mL) was stirred at RT overnight. The mixture was diluted with water (10 mL) and extracted with DCM (10 mL*3). The combined organic layer was washed with brine (20 mL), dried over Na_2SO_4, filtered and concentrated in-vacuo. The residue was purified by *prep*-HPLC to afford (R)-N-(4-(3-((4-amino-5-chloropyrimidin-2-yl)amino)pyrrolidine-1-carbonyl)phenyl)acrylamide (34.0 mg, 11%) as a white solid (TFA salt). ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.95-2.02 (m, 1H), 2.14-2.27 (m, 1H), 3.40-3.82 (m, 3H), 4.25-4.48 (m, 1H), 5.79 (d, J = 10.4 Hz, 1H), 6.26 (s, 0.5H), 6.30 (s, 0.5H), 6.41-6.48 (m, 1H), 7.51-7.53 (m, 2H), 7.70-7.75 (m, 2H), 8.00-8.39 (m, 4H), 10.32 (s, 1H). [M+H] Calc'd for $C_{18}H_{20}ClN_6O_2$, 387.1; Found, 387.1

Example 91: Synthesis of (R)-N-(4-(3-((4-amino-5-(trifluoromethyl)pyrimidin-2-yl)amino)pyrrolidine-1-carbonyl)phenyl)acrylamide



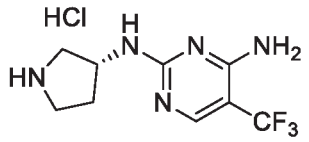
Step 1: (R)-tert-butyl 3-((4-amino-5-(trifluoromethyl)pyrimidin-2-yl)amino)pyrrolidine-1-carboxylate



[00460] To a mixture of 2-chloro-5-(trifluoromethyl)pyrimidin-4-amine (500 mg, 2.53 mmol) and (R)-tert-butyl 3-aminopyrrolidine-1-carboxylate (944 mg, 5.07 mmol) in DMSO (20 mL) was added K_2CO_3 (700 mg, 5.07 mmol). The mixture was stirred at 170°C for 1.5h in microwave. The mixture was cooled, diluted with water (10 mL) and extracted with DCM (10 mL* 3). The combined organic layer was washed with brine (20 mL), dried over Na_2SO_4, filtered and concentrated *in vacuo*. The residue was purified by column (PE:EA = 3:1) to afford (R)-tert-butyl 3-((4-amino-5-

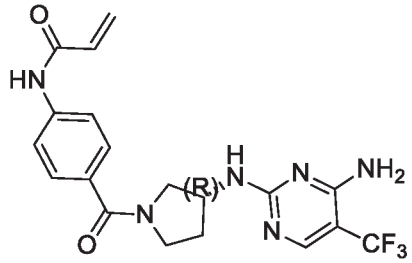
(trifluoromethyl)pyrimidin-2-yl)amino)pyrrolidine-1-carboxylate (920 mg, 87%) as a white solid. [M+H] Calc'd for $C_{14}H_{21}F_3N_5O_2$, 348.1; Found, 348.1

Step 2: (R)-N2-(pyrrolidin-3-yl)-5-(trifluoromethyl)pyrimidine-2,4-diamine (HCl salt)



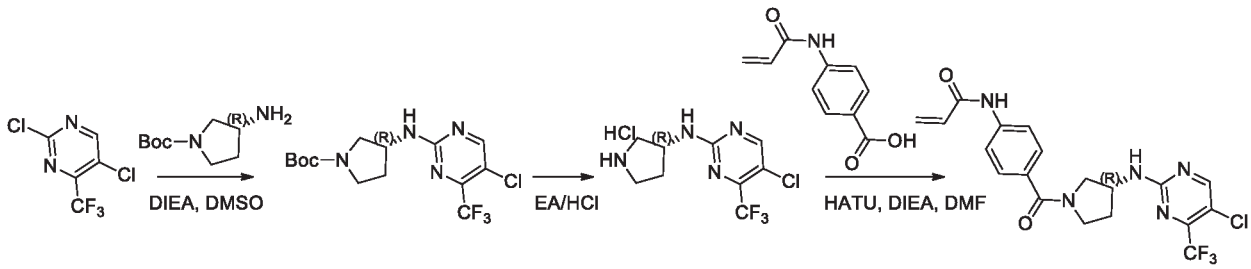
[00461] A mixture of (R)-tert-butyl 3-((4-amino-5-(trifluoromethyl)pyrimidin-2-yl)amino)pyrrolidine-1-carboxylate (920 mg, 2.65 mmol) in HCl/EA (15 mL) was stirred at RT for 3 h. The reaction mixture was concentrated *in vacuo* to afford (R)-N2-(pyrrolidin-3-yl)-5-(trifluoromethyl)pyrimidine-2,4-diamine (HCl salt) (900 mg, >100%) as a white solid. [M+H] Calc'd for $C_9H_{12}F_3N_5$, 248.0; Found, 248.0

Step 3: (R)-N-(4-(3-((4-amino-5-(trifluoromethyl)pyrimidin-2-yl)amino)pyrrolidine-1-carbonyl)phenyl)acrylamide

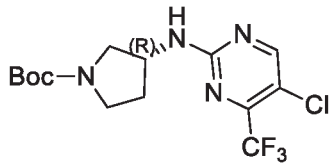


[00462] A mixture of 4-acrylamidobenzoic acid (200 mg, 1.05 mmol), (R)-N2-(pyrrolidin-3-yl)-5-(trifluoromethyl)pyrimidine-2,4-diamine (HCl salt) (888 mg, 3.14 mmol), HATU (477 mg, 1.25 mmol) and DIEA (675 mg, 5.23 mmol) in DMF (15 mL) was stirred at RT for overnight. The mixture was diluted with water (10 mL) and extracted with DCM (10 mL* 3). The combined organic layer was washed with brine (20 mL), dried over Na_2SO_4,filtered and concentrated in-vacuo. The residue was purified by *prep*-HPLC to afford (R)-N-(4-(3-((4-amino-5-(trifluoromethyl)pyrimidin-2-yl)amino)pyrrolidine-1-carbonyl)phenyl)acrylamide (207.0 mg, 47%) as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.82-2.00 (m, 1H), 2.06-2.16 (m, 1H), 3.34-3.78 (m, 4H), 4.30-4.44 (m, 1H), 5.79 (d, J = 10.0 Hz, 1H), 6.26 (s, 0.5H), 6.30 (s, 0.5H), 6.41-6.48 (m, 1H), 6.66-6.86 (m, 2H), 7.35-7.65 (m, 3H), 7.68-7.75 (m, 2H), 8.00-8.14 (m, 1H), 10.32 (s, 1H). [M+H] Calc'd for $C_{19}H_{20}F_3N_6O_2$, 421.1; Found, 421.1.

Example 92: Synthesis of (R)-N-(4-(3-((5-chloro-4-(trifluoromethyl)pyrimidin-2-yl)amino)pyrrolidine-1-carbonyl)phenyl)acrylamide

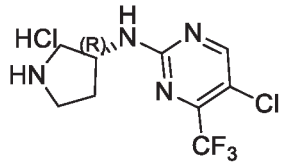


Step 1: (R)-tert-butyl 3-((5-chloro-4-(trifluoromethyl)pyrimidin-2-yl)amino)pyrrolidine-1-carboxylate



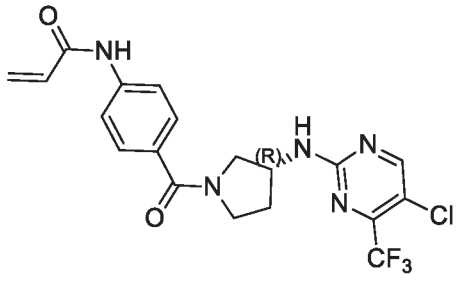
[00463] To a mixture of 2,5-dichloro-4-(trifluoromethyl)pyrimidine (500 mg, 2.7 mmol) and (R)-tert-butyl 3-aminopyrrolidine-1-carboxylate (643 mg, 3.5 mmol) in DMSO (10 mL) was added DIEA (593 mg, 4.6 mmol). The reaction mixture was stirred at RT for 16h. The mixture was diluted with water (10 mL) and extracted with DCM (10 mL*3). The combined organic layer was washed with brine (20 mL), dried over Na_2SO_4, filtered and concentrated in-vacuo. The residue was purified by column (PE:EA = 5:1) to afford (R)-tert-butyl 3-((5-chloro-4-(trifluoromethyl)pyrimidin-2-yl)amino)pyrrolidine-1-carboxylate (860 mg, 87%) as white solid. [M+H] Calc'd for $C_{14}H_{18}ClF_3N_4O_2$, 367.1; Found, 367.1

Step 2: (R)-5-chloro-N-(pyrrolidin-3-yl)-4-(trifluoromethyl)pyrimidin-2-amine hydrochloride



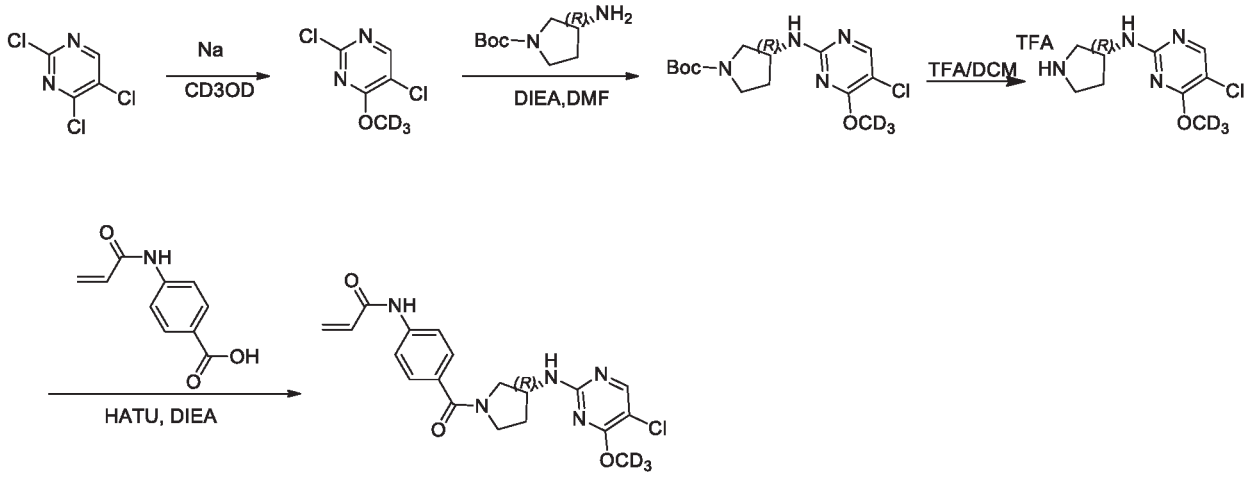
[00464] A mixture of (R)-tert-butyl 3-((5-chloro-4-(trifluoromethyl)pyrimidin-2-yl)amino)pyrrolidine-1-carboxylate (400 mg, 1.1 mmol) in HCl/EA (15 mL) was stirred at RT for 2h. The reaction mixture was concentrated to afford (R)-5-chloro-N-(pyrrolidin-3-yl)-4-(trifluoromethyl)pyrimidin-2-amine hydrochloride (342 mg, >100%) as white solid. [M+H] Calc'd for $C_9H_{11}Cl_2F_3N_4$, 267.1; Found, 267.1

Step 3: (R)-N-(4-(3-((5-chloro-4-(trifluoromethyl)pyrimidin-2-yl)amino)pyrrolidine-1-carbonyl)phenyl)acrylamide

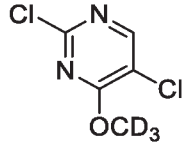


[00465] A mixture of 4-acrylamidobenzoic acid (207 mg, 1.1 mmol), (R)-5-chloro-N-(pyrrolidin-3-yl)-4-(trifluoromethyl)pyrimidin-2-amine hydrochloride (342 mg, 1.3 mmol), HATU (627 mg, 1.7 mmol) and DIEA (568 mg, 4.4 mmol) in DMF (10 mL) was stirred at RT for overnight. The mixture was diluted with water (10 mL) and extracted with DCM (10 mL* 3). The combined organic layer was washed with brine (20 mL), dried over Na_2SO_4, filtered and concentrated *in vacuo*. The residue was purified by *prep*-HPLC to afford (R)-N-(4-(3-((5-chloro-4-(trifluoromethyl)pyrimidin-2-yl)amino)pyrrolidine-1-carbonyl)phenyl)acrylamide (267.8 mg, 47%) as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.91-2.16 (m, 2H), 3.41-3.81 (m, 4H), 4.30-4.46 (m, 1H), 5.77-5.80 (m, 1H), 6.26-6.30 (m, 1H), 6.41-6.44 (m, 1H), 7.49-7.54 (m, 2H), 7.69-7.73 (m, 2H), 8.46 (s, 1H), 8.62-8.70 (m, 1H), 10.29 (s, 1H). [M+H] Calc'd for $C_{19}H_{17}ClF_3N_5O_2$, 440.1; Found, 440.1

Example 93: Synthesis of (R)-N-(4-(3-((5-chloro-4-(trideuteromethoxy)pyrimidin-2-yl)amino)pyrrolidine-1-carbonyl)phenyl)acrylamide



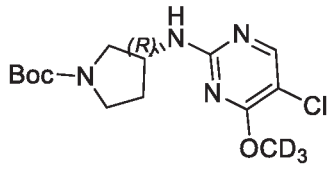
Step 1: 2,5-dichloro-4-(trideuteromethoxy)pyrimidine



[00466] Na (186 mg, 8.07 mmol) was added portionwise into CD_3OD (2.0 mL) at RT. After addition, the mixture was stirred at RT for another 2 hours. Then a solution of 2,4,5-trichloropyrimidine (1.0 g, 5.45 mmol) in THF (10 mL) was added into above mixture and the reaction mixture was stirred at

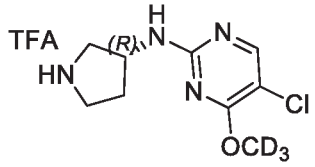
RT for overnight. The mixture was concentrated and the residue was purified by flash chromatography on silica gel (PE) to afford 2,5-dichloro-4-(trideuteromethoxy)pyrimidine (900 mg, 92%) as a white solid. [M+H] Calc'd for $C_5HD_3Cl_2N_2O$, 181.9; Found, 181.9.

Step 2: (R)-tert-butyl 3-((5-chloro-4-(trideuteromethoxy)pyrimidin-2-yl)amino)pyrrolidine-1-carboxylate



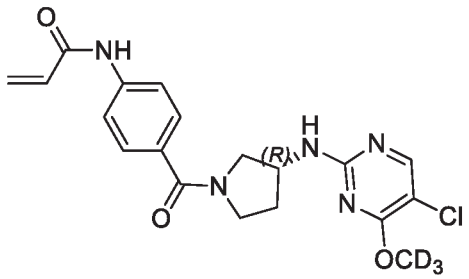
[00467] The title compound was prepared in 76% yield from (R)-tert-butyl 3-aminopyrrolidine-1-carboxylate using general procedure of (*R*)-*tert*-butyl 3-((5-chloro-4-methylpyrimidin-2-yl)amino)pyrrolidine-1-carboxylate. [M+H] Calc'd for $C_{14}H_{18}D_3ClN_4O_3$, 332.1; Found, 332.1.

Step 3: (R)-5-chloro-N-(pyrrolidin-3-yl)-4-(trichloromethoxy)pyrimidin-2-amine 2,2,2-trifluoroacetate



[00468] The title compound was prepared in 100% yield from (R)-tert-butyl 3-((5-chloro-4-(trideuteromethoxy)pyrimidin-2-yl)amino)pyrrolidine-1-carboxylate using general procedure of (*R*)-5-chloro-4-methyl-N-(pyrrolidin-3-yl)pyrimidin-2-amine 2,2,2-trifluoroacetate. [M+H] Calc'd for $C_9H_{10}D_3ClN_4O$, 232.0; Found, 232.0.

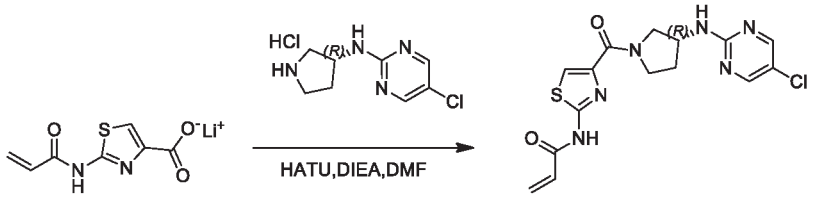
Step 4: (R)-N-(4-(3-((5-chloro-4-(trideuteromethoxy)pyrimidin-2-yl)amino)pyrrolidine-1-carbonyl)phenyl)acrylamide



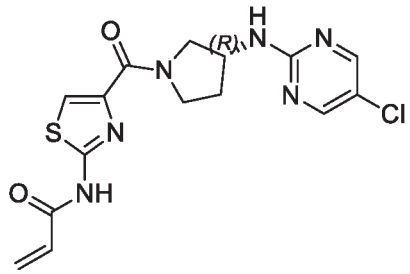
[00469] The title compound was prepared in 20% yield from (R)-5-chloro-N-(pyrrolidin-3-yl)-4-(trichloromethoxy)pyrimidin-2-amine 2,2,2-trifluoroacetate using general procedure of (*R*)-*N*-(4-(3-((5-chloro-4-methylpyrimidin-2-yl)amino)pyrrolidine-1-carbonyl)phenyl)acrylamide. ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.85-2.01 (m, 1H), 2.07-2.15 (m, 1H), 3.42-3.79 (m, 4H), 4.26-4.42 (m, 1H), 5.74-5.80 (m, 1H), 6.28 (d, J = 16.4 Hz, 1H), 6.45-6.49 (m, 1H), 7.47-7.53 (m, 2H),

7.68-7.73 (m, 3H), 8.07 (s, 0.5H), 8.14 (s, 0.5H) 10.29 (s, 1H). [M+H] Calc'd for $C_{19}H_{17}D_3ClN_5O_3$, 405.1; Found, 405.1.

Example 94: Synthesis of (*R*)-*N*-(4-(3-((5-chloropyrimidin-2-yl)amino)pyrrolidine-1-carbonyl)thiazol-2-yl)acrylamide

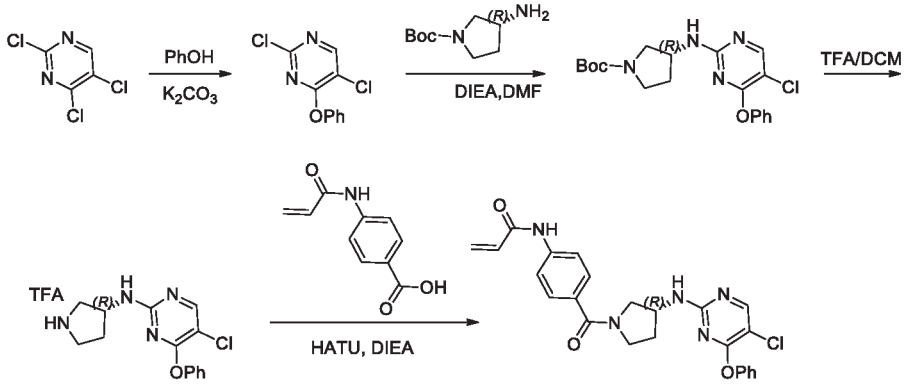


Step 1: (R)-N-(4-(3-((5-chloropyrimidin-2-yl)amino)pyrrolidine-1-carbonyl)thiazol-2-yl)acrylamide

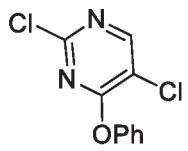


[00470] The title compound was prepared in 20% yield from lithium 2-acrylamidothiazole-4-carboxylate using general procedure of (*R*)-*N*-(4-(3-((5-chloro-4-methylpyrimidin-2-yl)amino)pyrrolidine-1-carbonyl)phenyl)acrylamide. ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.89-2.00 (m, 1H), 2.07-2.21 (m, 1H), 3.47-3.56 (m, 1H), 3.65-3.71 (m, 1H), 3.74-3.79 (m, 0.5H), 3.92-3.98 (m, 1H), 4.10-4.15 (m, 0.5H), 4.33-4.39 (m, 1H), 5.89-5.94 (m, 1H), 6.37-6.43 (m, 1H), 6.50-6.58 (m, 1H), 7.75 (d, J = 2.0 Hz, 1H), 7.83 (d, J = 6.4 Hz, 1H), 8.32 (s, 1H), 8.38 (s, 1H), 12.38 (br s, 1H). [M+H] Calc'd for $C_{15}H_{15}ClN_6O_2S$, 379.0; Found, 379.0.

Example 95: Synthesis of (*R*)-*N*-(4-(3-((5-chloro-4-phenoxypyrimidin-2-yl)amino)pyrrolidine-1-carbonyl)phenyl)acrylamide

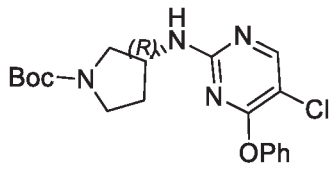


Step 1: 2,5-dichloro-4-phenoxypyrimidine



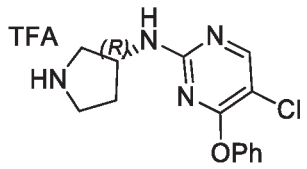
[00471] A solution of 2,4,5-trichloropyrimidine (500 mg, 2.72 mmol), phenol (384 mg, 4.08 mmol) and K_2CO_3 (750 mg, 5.44 mmol) in DMF (5 mL) was stirred at RT for 4 hours. The mixture was diluted with water (20 mL) and extracted with EtOAc (30 mL*2). The combined organic phase was washed with brine (20 mL), dried over Na_2SO_4, filtered and concentrated to afford 2,5-dichloro-4-phenoxypyrimidine (700 mg, crude, 100%) as a white solid. [M+H] Calc'd for $C_{10}H_6Cl_2N_2O$, 240.9; Found, 240.9.

Step 2: (R)-tert-butyl 3-((5-chloro-4-phenoxypyrimidin-2-yl)amino)pyrrolidine-1-carboxylate



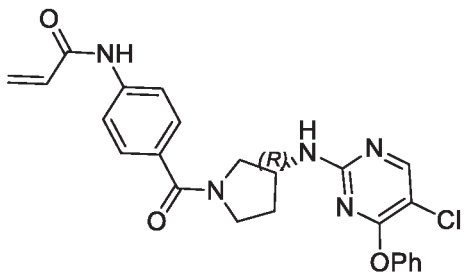
The title compound was prepared in 56% yield from 2,5-dichloro-4-phenoxypyrimidine using general procedure of (*R*)-*tert*-butyl 3-((5-chloro-4-methylpyrimidin-2-yl)amino)pyrrolidine-1-carboxylate. [M+H] Calc'd for $C_{19}H_{23}ClN_4O_3$, 391.1; Found, 391.1.

Step 3: (R)-5-chloro-4-phenoxy-N-(pyrrolidin-3-yl)pyrimidin-2-amine 2,2,2-trifluoroacetate



[00472] The title compound was prepared in 100% yield from (*R*)-*tert*-butyl 3-((5-chloro-4-phenoxypyrimidin-2-yl)amino)pyrrolidine-1-carboxylate using general procedure of (*R*)-5-chloro-4-methyl-N-(pyrrolidin-3-yl)pyrimidin-2-amine 2,2,2-trifluoroacetate. [M+H] Calc'd for $C_{14}H_{15}ClN_4O$, 291.0; Found, 291.0.

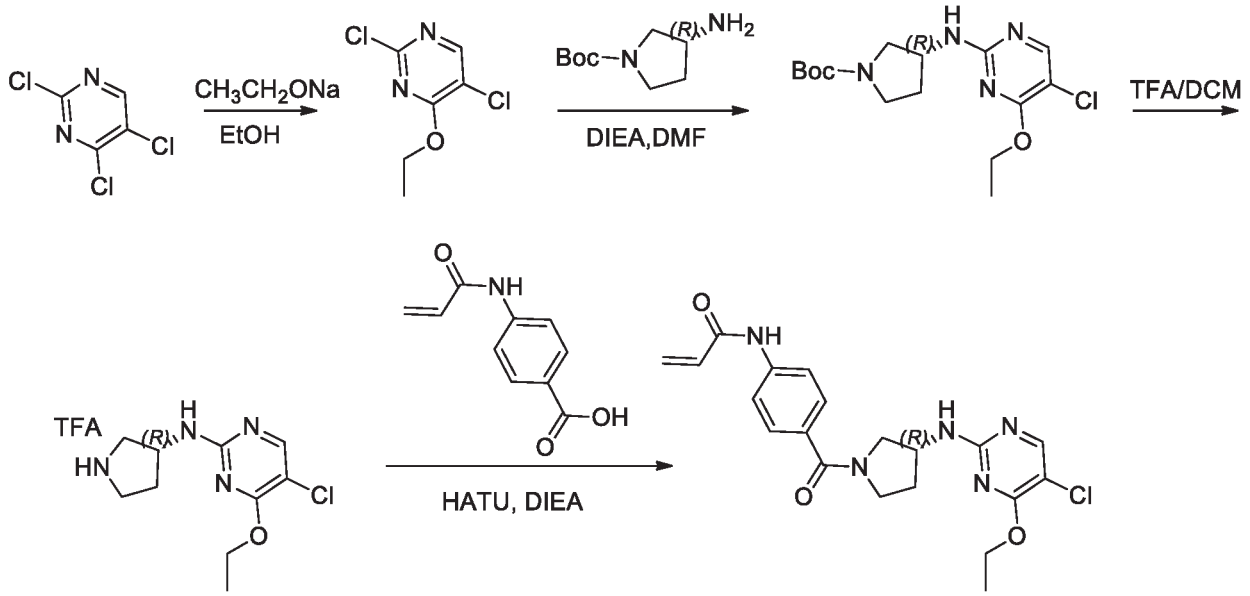
Step 4: (*R*)-*N*-(4-(3-((5-chloro-4-phenoxypyrimidin-2-yl)amino)pyrrolidine-1-carbonyl)phenyl)acrylamide



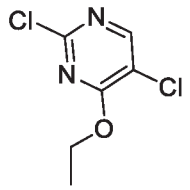
[00473] The title compound was prepared in 20% yield from (R)-5-chloro-4-phenoxy-N-(pyrrolidin-3-yl)pyrimidin-2-amine 2,2,2-trifluoroacetate using general procedure of (*R*)-*N*-(4-(3-((5-chloro-4-

methylpyrimidin-2-yl)amino)pyrrolidine-1-carbonyl)phenyl)acrylamide. ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.85-2.15 (m, 2H), 3.30-3.32 (m, 1H), 3.36-3.73 (m, 3H), 4.23-4.38 (m, 1H), 5.78 (d, J = 1.2 Hz, 1H), 6.26 (s, 0.4H), 6.29 (s, 0.6H), 7.12-7.31 (m, 4H), 7.45-7.46 (m, 3H), 7.48-7.78 (m, 3H), 8.25 (s, 0.6H), 8.27 (s, 0.4H), 10.30 (s, 1H). [M+H] Calc'd for $C_{24}H_{22}ClN_5O_3$, 464.1; Found, 464.1.

Example 96: Synthesis of (*R*)-*N*-(4-(3-((5-chloro-4-ethoxypyrimidin-2-yl)amino)pyrrolidine-1-carbonyl)phenyl)acrylamide

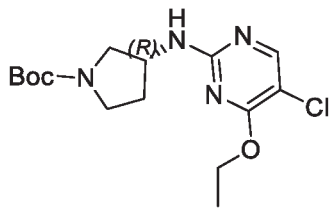


Step 1: 2,5-dichloro-4-ethoxypyrimidine



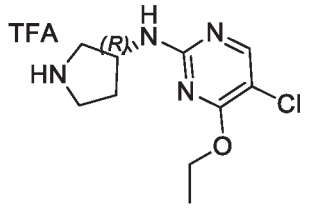
[00474] A solution of 2,4,5-trichloropyrimidine (1.00 g, 5.43 mmol) and CH_3CH_2ONa (0.73 g, 10.87 mmol) in EtOH (10 mL) was stirred at RT for 2 hours. The mixture was diluted with water (20 mL) and extracted with EtOAc (30 mL*2). The combined organic phase was washed with brine (30 mL), dried over Na_2SO_4, filtered and concentrated *in vacuo*. The residue was purified by flash chromatography on silica gel (PE/EtOAc = 10/1) to afford 2,5-dichloro-4-ethoxypyrimidine (0.95 g, 81%) as a white solid. [M+H] Calc'd for $C_6H_6Cl_2N_2O$, 192.9; Found, 192.9.

Step 2: (R)-tert-butyl 3-((5-chloro-4-ethoxypyrimidin-2-yl)amino)pyrrolidine-1-carboxylate



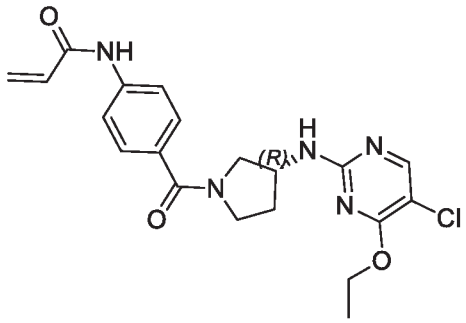
[00475] The title compound was prepared in 44% yield from 2,5-dichloro-4-ethoxypyrimidine using general procedure of (*R*)-*tert*-butyl 3-((5-chloro-4-methylpyrimidin-2-yl)amino)pyrrolidine-1-carboxylate. [M+H] Calc'd for $C_{15}H_{23}ClN_4O_3$, 343.1; Found, 343.1.

Step 3: (R)-5-chloro-4-ethoxy-N-(pyrrolidin-3-yl)pyrimidin-2-amine 2,2,2-trifluoroacetate



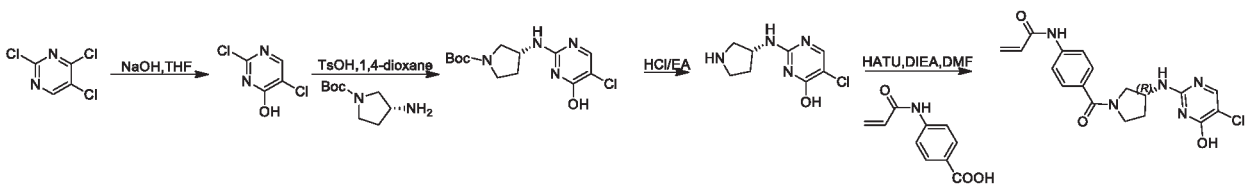
[00476] The title compound was prepared in 100% yield from (*R*)-*tert*-butyl 3-((5-chloro-4-ethoxypyrimidin-2-yl)amino)pyrrolidine-1-carboxylate using general procedure of (*R*)-5-chloro-4-methyl-N-(pyrrolidin-3-yl)pyrimidin-2-amine 2,2,2-trifluoroacetate. [M+H] Calc'd for $C_{10}H_{15}ClN_4O$, 243.0; Found, 243.0.

Step 4: (R)-N-(4-(3-((5-chloro-4-ethoxypyrimidin-2-yl)amino)pyrrolidine-1-carbonyl)phenyl)acrylamide

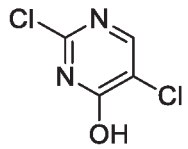


[00477] The title compound was prepared in 24% yield from (R)-5-chloro-4-ethoxy-N-(pyrrolidin-3-yl)pyrimidin-2-amine 2,2,2-trifluoroacetate using general procedure of (*R*)-*N*-(4-(3-((5-chloro-4-methylpyrimidin-2-yl)amino)pyrrolidine-1-carbonyl)phenyl)acrylamide. ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.26-1.39 (m, 3H), 1.93-2.17 (m, 2H), 3.41-3.82 (m, 4H), 4.26-4.45 (m, 3H), 5.80 (s, 0.5H), 5.83 (s, 0.5H), 6.28 (s, 0.4H), 6.33 (s, 0.6H), 6.43-6.52 (m, 1H), 7.51-7.57 (m, 2H), 7.71-7.77 (m, 3H), 8.10 (s, 0.6H), 8.17 (s, 0.4H), 10.35 (s, 1H). [M+H] Calc'd for $C_{20}H_{22}ClN_5O_3$, 416.1; Found, 416.1.

<u>Example 97: Synthesis of (R)-N-(4-(3-((5-chloro-4-hydroxypyrimidin-2-yl)amino)pyrrolidine-1-carbonyl)phenyl)acrylamide</u>

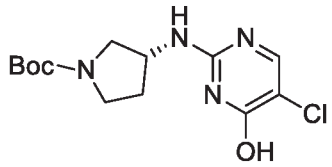


Step 1: 2,5-dichloropyrimidin-4-ol



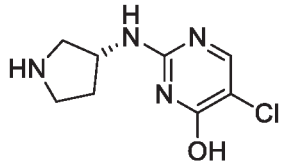
[00478] A mixture of 2,4,5-trichloropyrimidine (2.0 g, 10.9 mmol) and NaOH (872 mg, 21.8 mmol) in THF (10 mL) and water (1 mL) was stirred at RT overnight. The reaction mixture was added H_2O (40 mL) and extracted with EA (40 mL*2). The combined organic laye was dried over Na_2SO_4, filtered and concentrated to afford 2,5-dichloropyrimidin-4-ol (1.7 g, 95%) as a yellow solid. [M+H] Calc'd for $C_4H_2Cl_2N_2O$, 164.9; Found, 164.9

Step 2: (R)-tert-butyl 3-((5-chloro-4-hydroxypyrimidin-2-yl)amino)pyrrolidine-1-carboxyla te



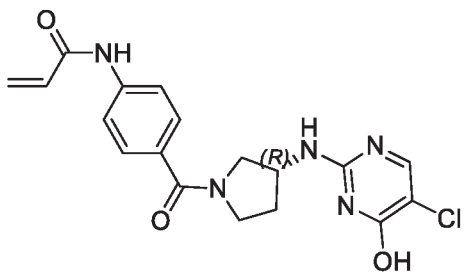
[00479] A mixture of 2,5-dichloropyrimidin-4-ol (800 mg, 4.9 mmol), (R)-tert-butyl 3-aminopyrrolidine-1-carboxylate (1.4 g, 7.3 mmol) and TsOH (1.4 g, 7.3 mmol) in 1,4-dioxane (25 mL) was stirred at 105°C overnight. The reaction mixture was concentrated and purified by prep-HPLC to afford (R)-tert-butyl 3-((5-chloro-4-hydroxypyrimidin-2-yl)amino)pyrrolidine-1-carboxylate (400 mg, 27%) as a white solid. [M+H] Calc'd for $C_{13}H_{19}ClN_4O_3$,315.1; Found, 315.1

Step 3: (R)-5-chloro-2-(pyrrolidin-3-ylamino)pyrimidin-4-ol



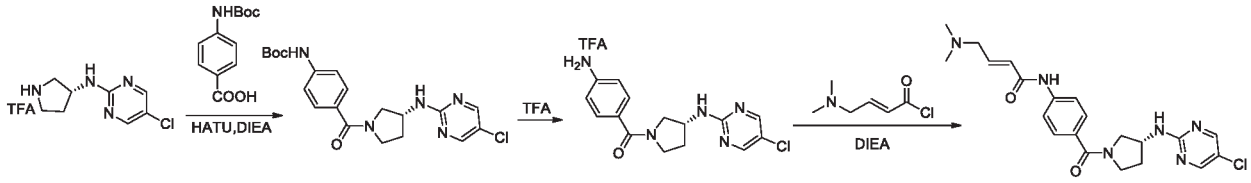
[00480] A mixture of (R)-tert-butyl 3-((5-chloro-4-hydroxypyrimidin-2-yl)amino)pyrrolidine-1-carboxylate (100 mg, 0.32 mmol) in HCl/EA (5 mL) was stirred at RT for 1h. The reaction mixture was concentrated *in vacuo* to afford (R)-5-chloro-2-(pyrrolidin-3-ylamino)pyrimidin-4-ol (50 mg, 74%) as yellow oil. [M+H] Calc'd for $C_8H_{11}ClN_4O$, 215.1; Found, 215.1

Step 4: (R)-N-(4-(3-((5-chloro-4-hydroxypyrimidin-2-yl)amino)pyrrolidine-1-carbonyl) phe nyl)acrylamide

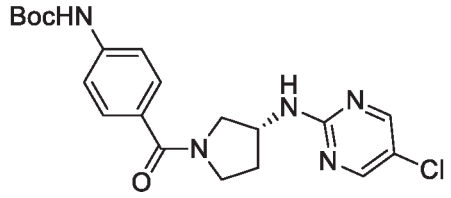


[00481] A mixture of (R)-5-chloro-2-(pyrrolidin-3-ylamino)pyrimidin-4-ol (200 mg, 0.93 mmol), 4-acrylamidobenzoic acid (196 mg, 1.0 mmol), HATU (353 mg, 0.93 mmol) and DIEA (241 mg, 1.8 mmol) in DMF (10 mL) was stirred at RT for overnight. To the reaction mixture was added H_2O (40 mL) and extracted with EA. The combind organic layer was dried over Na_2SO_4, filtered and concentrated. The residue was purified by prep-HPLC to afford (R)-N-(4-(3-((5-chloro-4-hydroxypyrimidin-2-yl)amino)pyrrolidine-1-carbonyl)phenyl)acrylamide (10.6 mg, 3%) as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ 2.00-2.02 (m, 1H), 2.15-2.20 (m, 1H), 3.45-3.70 (m, 4H), 4.54 (s, 1H), 5.77-5.80 (m, 1H), 6.31 (d, J = 2.0 Hz, 1H), 6.41-6.43 (m, 1H), 7.73 (d, J = 8.8 Hz, 2H), 7.82-7.85 (m, 3H), 8.49 (d, J = 6.4 Hz, 1H), 10.38 (s, 1H). [M+H] Calc'd for $C_{18}H_{18}ClN_5O_3$, 387.9; Found, 387.9.

Example 98: Synthesis of (*R*,*E*)-*N*-(4-(3-((5-chloropyrimidin-2-yl)amino)pyrrolidine-1-carbonyl)phenyl)-4-(dimethylamino)but-2-enamide

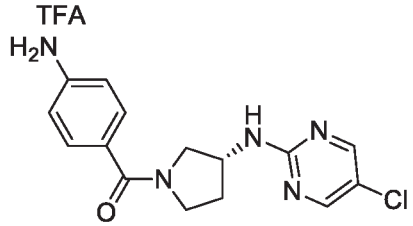


Step 1: (R)-tert-butyl (4-(3-((5-chloropyrimidin-2-yl)amino)pyrrolidine-1-carbonyl)phenyl)carbamate



[00482] The title compound was prepared in 74% yield from (*R*)-5-chloro-*N*-(pyrrolidin-3-yl)pyrimidin-2-amine 2,2,2-trifluoroacetate using general procedure of (*R*)-*N*-(4-(3-((5-chloro-4-methylpyrimidin-2-yl)amino)pyrrolidine-1-carbonyl)phenyl)acrylamide. [M+H] Calc'd for $C_{20}H_{24}ClN_5O_3$, 418.1; Found, 418.1.

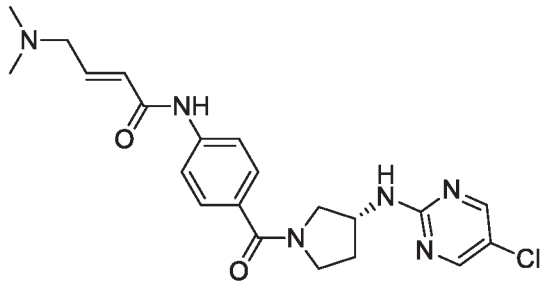
Step 2: (R)-(4-aminophenyl)(3-((5-chloropyrimidin-2-yl)amino)pyrrolidin-1-yl)methanone 2,2,2-trifluoroacetate



[00483] The title compound was prepared in 100% yield from (*R*)-*tert*-butyl (4-(3-((5-chloropyrimidin-2-yl)amino)pyrrolidine-1-carbonyl)phenyl)carbamateusing general procedure of (*R*)-5-chloro-4-

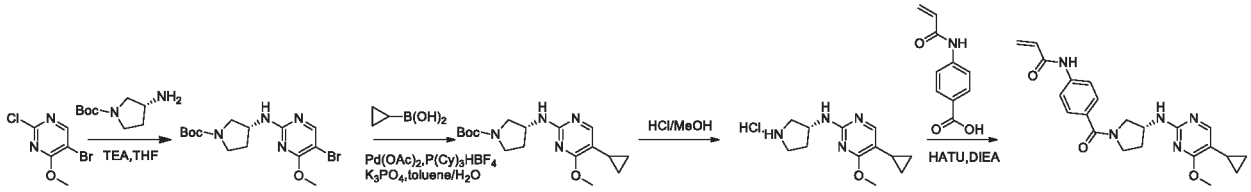
methyl-N-(pyrrolidin-3-yl)pyrimidin-2-amine 2,2,2-trifluoroacetate. [M+H] Calc'd for $C_{15}H_{16}ClN_5O$, 318.0; Found, 318.0.

Step 3: (R,E)-N-(4-(3-((5-chloropyrimidin-2-yl)amino)pyrrolidine-1-carbonyl)phenyl)-4-(dimethylamino)but-2-enamide

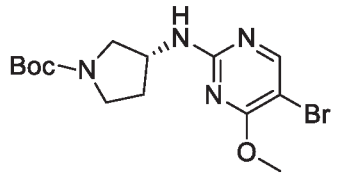


[00484] The title compound was prepared in 20% yield from (R)-(4-aminophenyl)(3-((5-chloropyrimidin-2-yl)amino)pyrrolidin-1-yl)methanone general procedure of (R)-1-(6-(3-((5-chloro-4-methoxypyrimidin-2-yl)amino)pyrrolidine-1-carbonyl)-2-azaspiro[3.3]heptan-2-yl)prop-2-en-1-one. ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.88-2.01 (m, 1H), 2.10-2.12 (m, 1H), 2.18 (s, 6H), 3.05 (d, J = 5.2 Hz, 2H), 3.36-3.45 (m, 1H), 3.51-3.57 (m, 1H), 3.64-3.74 (m, 1H), 3.76-3.78 (m, 1H), 4.24-4.40 (m, 1H), 6.28 (d, J = 15.2 Hz, 1H), 6.72-6.78 (m, 1H), 7.47-7.52 (m, 2H), 7.67-7.71 (m, 2H), 7.79-7.81 (m, 1H), 8.31 (s, 1H), 8.38 (s, 1H), 10.21 (s, 1H). [M+H] Calc'd for $C_{21}H_{25}ClN_6O_2$, 429.1; Found, 429.1.

Example 99: Synthesis of (*R*)-*N*-(4-(3-((5-cyclopropyl-4-methoxypyrimidin-2-yl)amino)pyrrolidine-1-carbonyl)phenyl)acrylamide



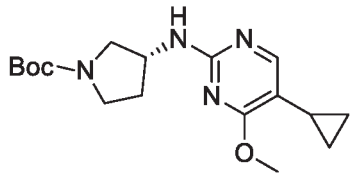
Step 1: (R)-tert-butyl 3-((5-bromo-4-methoxypyrimidin-2-yl)amino)pyrrolidine-1-carboxylate



[00485] A mixture of 5-bromo-2-chloro-4-methoxypyrimidine (2.5 g, 13.4 mmol), (*R*)-*tert*-butyl 3-aminopyrrolidine-1-carboxylate (3.0 g, 13.4 mmol) and TEA (4.0 g, 40.2 mmol) in THF (30 mL) was stirred at 80°C for 16 hours. The mixture was cooled to RT, diluted with water (50 mL) and extracted with EtOAc (50 mL*3). The combined organic phase was washed with brine (50 mL), dried over Na_2SO_4, filtered and concentrated *in vacuo*. The residue was purified by flash chromatography on silica gel (PE/EtOAc = 2/1) to afford (R)-tert-butyl 3-((5-bromo-4-

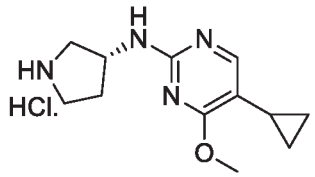
methoxypyrimidin-2-yl)amino)pyrrolidine-1-carboxylate (2.3 g, 46%) as a white solid. [M+H] Calc'd for $C_{14}H_{21}BrN_4O_3$, 373.0 ; Found, 373.0.

Step 2: (R)-tert-butyl 3-((5-cyclopropyl-4-methoxypyrimidin-2-yl)amino)pyrrolidine-1-carboxylate



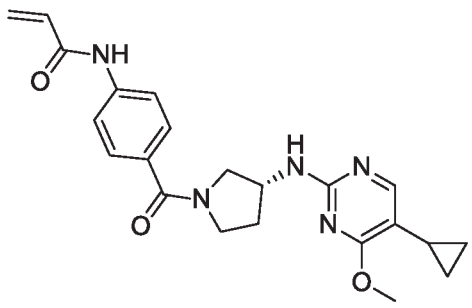
[00486] A mixture of (R)-tert-butyl 3-((5-bromo-4-methoxypyrimidin-2-yl)amino)pyrrolidine-1-carboxylate (200 mg, 0.54 mmol), cyclopropylboronic acid (230 mg, 2.68 mmol), $Pd(OAc)_2$, (73 mg, 0.32 mmol), $P(Cy)_3HBF_4$ (48 mg, 0.13 mmol) and K_3PO_4 (1.14 g, 5.41 mmol) in toluene/H_2O (20 mL/ 2 mL) was stirred at 100°C under N_2 for 4 hours. The mixture was cooled to RT and filtered over Celite. The filtrate was concentrated *in vacuo* and the residue was purified by flash chromatography on silica gel (PE/EtOAc = 10/1 to PE/EtOAc = 3/1) to afford (*R*)-*tert*-butyl 3-((5-cyclopropyl-4-methoxypyrimidin-2-yl)amino)pyrrolidine-1-carboxylate (150 mg, 83%) as colorless oil. [M+H] Calc'd for $C_{17}H_{26}N_4O_3$, 335.2; Found, 335.2.

Step 3: (R)-5-cyclopropyl-4-methoxy-N-(pyrrolidin-3-yl)pyrimidin-2-amine



[00487] The title compound was prepared in 100% yield from (*R*)-*tert*-butyl 3-((5-cyclopropyl-4-methoxypyrimidin-2-yl)amino)pyrrolidine-1-carboxylate using general procedure of (*R*)-5-chloro-4-methyl-*N*-(pyrrolidin-3-yl)pyridin-2-amine hydrochloride. [M+H] Calc'd for $C_{12}H_{18}N_4O$, 235.1; Found, 235.1.

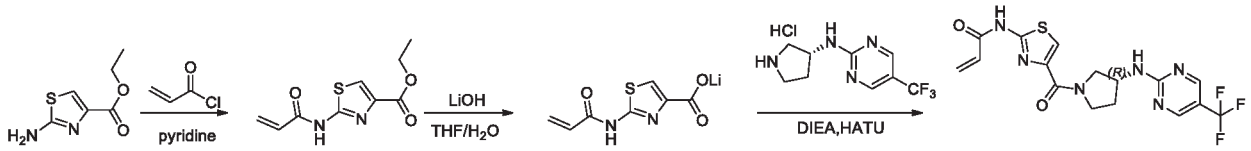
Step 4: (R)-N-(4-(3-((5-cyclopropyl-4-methoxypyrimidin-2-yl)amino)pyrrolidine-1-carbonyl)phenyl)acrylamide



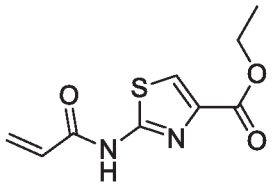
[00488] The title compound was prepared in 13% yield from (*R*)-5-cyclopropyl-4-methoxy-*N*-(pyrrolidin-3-yl)pyrimidin-2-amine hydrochloride using general procedure of (*R*)-*N*-(4-(3-((5-chloro-4-

methylpyrimidin-2-yl)amino)pyrrolidine-1-carbonyl)phenyl)acrylamide. ^{1}H NMR (400 MHz, DMSO-d_6): δ 0.50-0.55 (m, 2H), 0.69-0.76 (m, 2H), 1.59-1.68 (m, 1H), 1.86-2.01 (m, 1H), 2.07-2.16 (m, 1H), 3.36-3.43 (m, 1H), 3.46-3.55 (m, 1H), 3.60-3.69 (m, 1H), 3.73-3.75 (m, 1H), 3.80 (s, 1.5H), 3.89 (s, 1.5H), 4.22-4.43 (m, 1H), 5.79 (d, J = 10.0 Hz, 1H), 6.28 (d, J = 16.8 Hz, 1H), 6.41-6.47 (m, 1H), 7.19-7.23 (m, 1H), 7.48-7.54 (m, 2H), 7.67-7.75 (m, 3H), 10.31 (s, 1H). [M+H] Calc'd for $C_{22}H_{25}N_5O_3$, 408.1 ; Found, 408.1.

Example 100: Synthesis of (*R*)-*N*-(4-(3-((5-(trifluoromethyl)pyrimidin-2-yl)amino)pyrrolidine-1-carbonyl)thiazol-2-yl)acrylamide

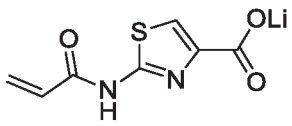


Step 1: ethyl 2-acrylamidothiazole-4-carboxylate



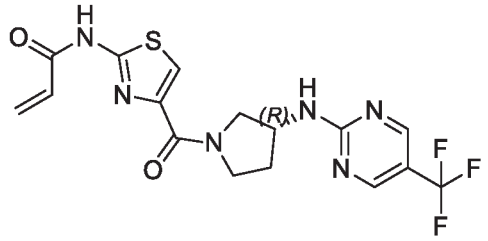
[00489] To a solution of ethyl 2-aminothiazole-4-carboxylate (3.0 g, 17.4 mmol) in DMF (20 mL) was added pyridine (1.5 g, 19.1mmol) and acryloyl chloride (2.4 g, 28.1 mmol) at 0°C. The reaction mixture was stiired at 0°C for 10 minutes and then at RT for overnight. The mixture was poured into ice-water (30 mL) and extracted with EtOAc (30 mL*5). The combined organic phase was washed with brine (30 mL*2), dried over Na_2SO_4, filtered and concentrated *in vacuo*. The residue was purified by flash chromatography on silica gel (petroleum ether/EtOAc = 3/1) to afford ethyl 2-acrylamidothiazole-4-carboxylate (1.0 g, 25%) as a white solid. [M+H] Calc'd for $C_9H_{10}N_2O_3S$, 227.0; Found, 227.0.

Step 2: lithium 2-acrylamidothiazole-4-carboxylate



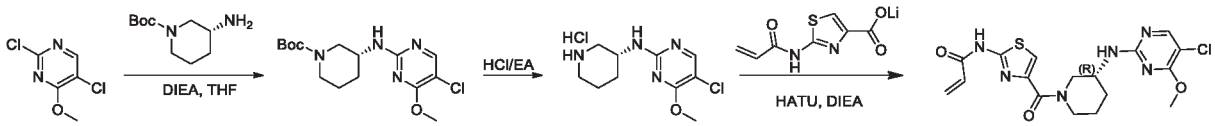
[00490] To a solution of ethyl 2-acrylamidothiazole-4-carboxylate (300 mg, 1.6 mmol) in THF/H_2O (4 mL/2 mL) was added LiOH·H_2O (56 mg, 1.3 mmol). The mixture was stiired at RT for overnight. Another batch of LiOH·H_2O (56 mg, 1.3 mmol) was added. The mixture was stired at RT for 5 hours. The mixture was concentrated *in vacuo* to afford lithium 2-acrylamidothiazole-4-carboxylate (326 mg,crude, 100%) as a yellow solid. [M+H] Calc'd for $C_7H_5LiN_2O_3S$, 199.0; Found, 199.0

Step 3: (R)-N-(4-(3-((5-(trifluoromethyl)pyrimidin-2-yl)amino)pyrrolidine-1-carbonyl)thiazol-2-yl)acrylamide

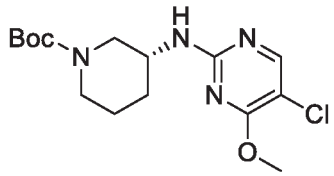


[00491] The title compound was prepared in 30% yield from lithium 2-acrylamidothiazole-4-carboxylate using general procedure of (*R*)-*N*-(4-(3-((5-chloro-4-methylpyrimidin-2-yl)amino)pyrrolidine-1-carbonyl)phenyl)acrylamide. ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.99-2.07 (m, 1H), 2.13-2.23 (m, 1H), 3.50-3.58 (m, 1H), 3.68-3.73 (m, 1H), 3.78-3.83 (m, 0.5H), 3.93-3.99 (m, 1H), 4.14-4.18 (m, 0.5H), 4.46-4.52 (m, 1H), 5.89-5.93 (m, 1H), 6.37-6.43 (m, 1H), 6.50-6.58 (m, 1H), 7.75 (s, 1H), 8.40 (d, *J* = 6.4 Hz, 1H), 8.65-8.70 (m, 2H), 12.30 (br s, 1H). [M+H] Calc'd for $C_{16}H_{15}F_3N_6O_2S$, 413.0; Found, 413.0.

Example 101: Synthesis of (*R*)-*N*-(4-(3-((5-chloro-4-methoxypyrimidin-2-yl)amino)piperidine-1-carbonyl)thiazol-2-yl)acrylamide

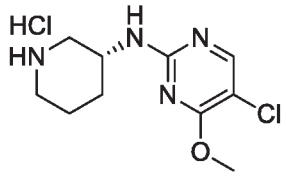


Step 1: (R)-tert-butyl 3-((5-chloro-4-methoxypyrimidin-2-yl)amino)piperidine-1-carboxylate



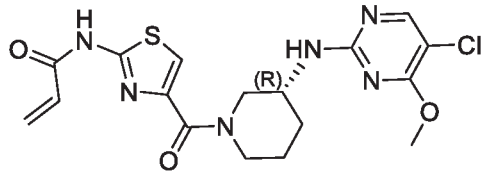
[00492] A mixture of 2,5-dichloro-4-methoxypyrimidine (300 mg, 1.7 mmol), (*R*)-*tert*-butyl 3-aminopiperidine-1-carboxylate (340 mg, 1.7 mmol) and DIEA (439 mg, 3.4 mmol) in THF (3 mL) was stirred at 80°C overnight. The mixture was cooled to RT, diluted with water (10 mL) and extracted with EtOAc (20 mL*3). The combined organic phase was washed with brine (20 mL), dried over Na_2SO_4, filtered and concentrated *in vacuo*. The residue was purified by flash chromatography on silica gel (petroleum ether/EtOAc = 5/1) to afford (R)-tert-butyl 3-((5-chloro-4-methoxypyrimidin-2-yl)amino)piperidine-1-carboxylate (188 mg, 33%) as yellow oil. [M+H] Calc'd for $C_{15}H_{23}ClN_4O_3$, 343.1; Found, 343.1.

Step 2: (R)-5-chloro-4-methoxy-N-(piperidin-3-yl)pyrimidin-2-amine hydrochloride



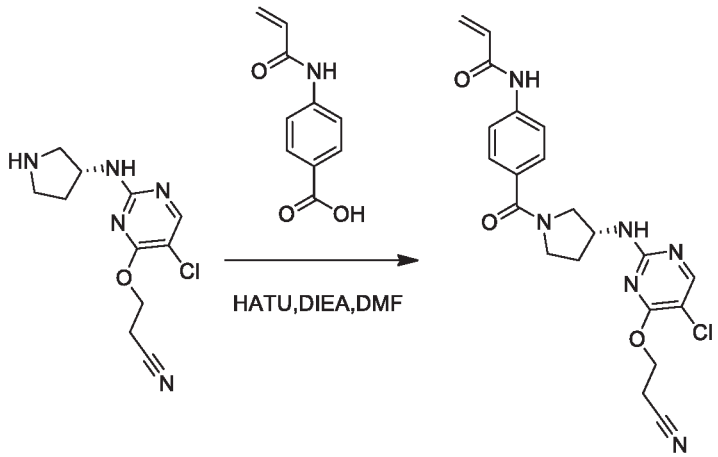
[00493] The title compound was prepared in 100% yield from (R)-tert-butyl 3-((5-chloro-4-methoxypyrimidin-2-yl)amino)piperidine-1-carboxylate using general procedure of (*R*)-5-chloro-4-methyl-*N*-(pyrrolidin-3-yl)pyridin-2-amine hydrochloride. [M+H] Calc'd for $C_{10}H_{15}ClN_4O$, 243.0; Found, 243.0.

Step 3: (R)-N-(4-(3-((5-chloro-4-methoxypyrimidin-2-yl)amino)piperidine-1-carbonyl)thiazol-2-yl)acrylamide



[00494] The title compound was prepared in 31% yield from (R)-5-chloro-4-methoxy-N-(piperidin-3-yl)pyrimidin-2-amine hydrochloride using general procedure of (*R*)-*N*-(4-(3-((5-chloro-4-methylpyrimidin-2-yl)amino)pyrrolidine-1-carbonyl)phenyl)acrylamide. ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.47-1.96 (m, 4H), 2.07-2.76 (m, 1H), 3.01-3.16 (m, 1H), 3.50-4.01 (m, 6H), 5.91 (d, *J* = 11.6 Hz, 1H), 6.38-6.52 (m, 2H), 7.23-7.44 (m, 2H), 7.93-8.10 (m, 1H), 12.40 (br s, 1H). [M+H] Calc'd for $C_{17}H_{19}ClN_6O_3S$, 423.0 ; Found, 423.0.

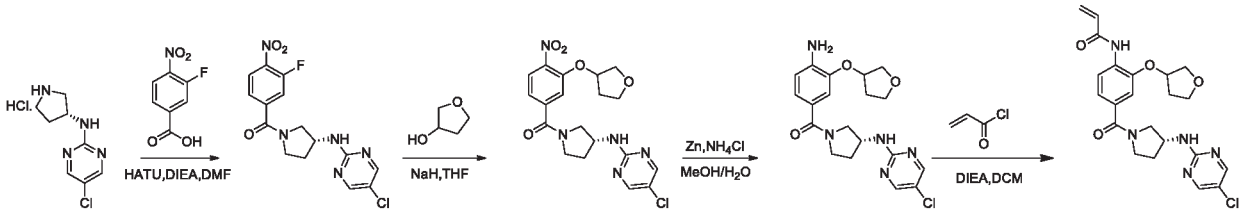
Example 102: Synthesis of (R)-N-(4-(3-((5-chloro-4-(2-cyanoethoxy)pyrimidin-2-yl)amino)pyrrolidine-1-carbonyl)phenyl)acrylamide



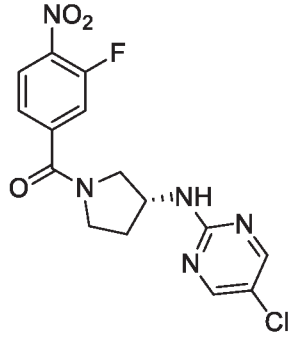
[00495] The title compound was prepared in 20% yield from (R)-3-((5-chloro-2-(pyrrolidin-3-ylamino)pyrimidin-4-yl)oxy)propanenitrile TFA salt using general procedure of (*R*)-*N*-(4-(3-((5-chloro-4-methylpyrimidin-2-yl)amino)pyrrolidine-1-carbonyl)phenyl)acrylamide. ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.90-2.01 (m, 1H), 2.07-2.15 (m, 1H), 2.99-3.09 (m, 2H), 3.39-3.45 (m, 1H),

3.51-3.54 (m, 1H),3.62-3.66 (m, 1H), 3.74-3.79 (m, 1H), 4.27-4.55 (m, 3H), 5.78 (d, J = 10.8 Hz, 1H), 6.26-6.30 (m, 1H), 6.41-6.48 (m, 1H), 7.49-7.54 (m, 2H), 7.69-7.73 (m, 3H), 8.13-8.20 (m, 1H), 10.30 (s, 1H). [M+H] Calc'd for $C_{21}H_{21}ClN_6O_3$, 441.1 ; Found, 441.1.

Example 103: Synthesis of *N*-(4-((*R*)-3-((5-chloropyrimidin-2-yl)amino)pyrrolidine-1-carbonyl)-2-((tetrahydrofuran-3-yl)oxy)phenyl)acrylamide

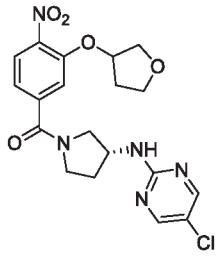


Step 1: (R)-(3-((5-chloropyrimidin-2-yl)amino)pyrrolidin-1-yl)(3-fluoro-4-nitrophenyl)methanone



[00496] The title compound was prepared in 77% yield from (R)-5-chloro-N-(pyrrolidin-3-yl)pyrimidin-2-amine hydrochloride using general procedure of (*R*)-*N*-(4-(3-((5-chloro-4-methylpyrimidin-2-yl)amino)pyrrolidine-1-carbonyl)phenyl)acrylamide. [M+H] Calc'd for $C_{15}H_{13}ClFN_5O_3$, 366.0 ; Found, 366.0.

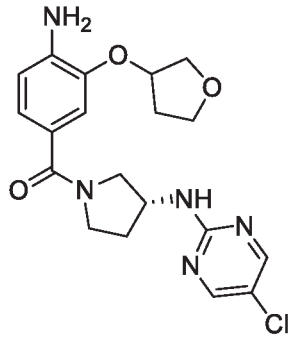
Step 2: ((R)-3-((5-chloropyrimidin-2-yl)amino)pyrrolidin-1-yl)(4-nitro-3-((tetrahydrofuran-3-yl)oxy)phenyl)methanone



[00497] To a solution of tetrahydrofuran-3-ol (24 mg, 0.27 mmol) in THF (5 mL) was added NaH (24 mg, 0.6 mmol, 60% wt in mineral oil) at 0°C. The mixture was stirred at 0°C under N_2 for 30 minutes. Then (R)-(3-((5-chloropyrimidin-2-yl)amino)pyrrolidin-1-yl)(3-fluoro-4-nitrophenyl)methanone (100 mg, 0.27 mmol) was added and the mixture was stirred at 0°C to RT under N_2 overnight. The mixture was diluted with water (10 mL) and extracted with EtOAc (20 mL*2). The combined

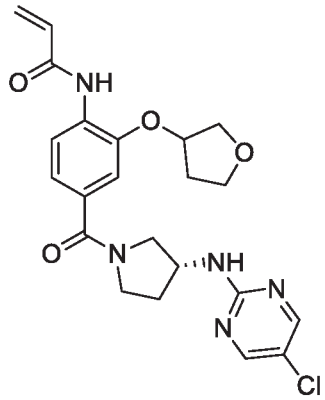
organic phase was washed with brine (20 mL), dried over Na_2SO_4, filtered and concentrated. The residue was purified by flash chromatography on silica gel (PE/EtOAc = 1/1) to afford ((R)-3-((5-chloropyrimidin-2-yl)amino)pyrrolidin-1-yl)(4-nitro-3-((tetrahydrofuran-3-yl)oxy)phenyl)methanone (100 mg, 85%) as yellow oil. [M+H] Calc'd for $C_{19}H_{20}ClN_5O_5$, 434.1; Found, 434.1.

Step 3: (4-amino-3-((tetrahydrofuran-3-yl)oxy)phenyl)((R)-3-((5-chloropyrimidin-2-yl)amino)pyrrolidin-1-yl)methanone



[00498] A mixture of ((R)-3-((5-chloropyrimidin-2-yl)amino)pyrrolidin-1-yl)(4-nitro-3-((tetrahydrofuran-3-yl)oxy)phenyl)methanone (100 mg, 0.23 mmol) and NH_4Cl (124 mg, 2.3 mmol) in MeOH (5 mL) and H_2O (2 mL) was heated to 50 °C for 10 minutes. Then Zn (150 mg, 2.3 mmol) was added. The mixture was stirred at 70 °C for 3 hours. The mixture was cooled to RT and filtered. The filtrate was concentrated *in vacuo*. The residue was diluted with water (10 mL) and extracted with EtOAc (20 mL*2). The combined organic phase was washed with brine (20 mL), dried over Na_2SO_4, filtered and concentrated to afford (4-amino-3-((tetrahydrofuran-3-yl)oxy)phenyl)((R)-3-((5-chloropyrimidin-2-yl)amino)pyrrolidin-1-yl)methanone (80 mg, 86%) as yellow oil. [M+H] Calc'd for $C_{19}H_{22}ClN_5O_3$, 404.1; Found, 404.1.

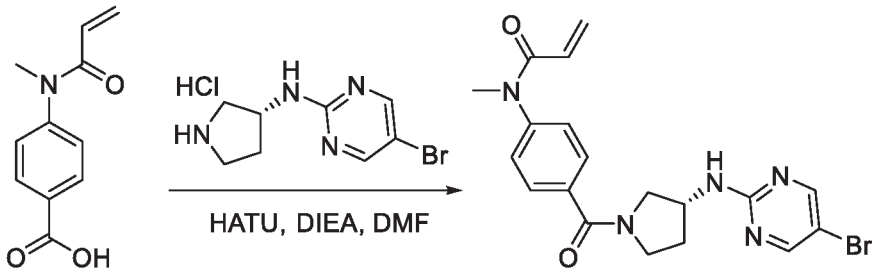
Step 4: N-(4-((R)-3-((5-chloropyrimidin-2-yl)amino)pyrrolidine-1-carbonyl)-2-((tetrahydrofuran-3-yl)oxy)phenyl)acrylamide



[00499] The title compound was prepared in 27% yield from (4-amino-3-((tetrahydrofuran-3-yl)oxy)phenyl)((R)-3-((5-chloropyrimidin-2-yl)amino)pyrrolidin-1-yl)methanone using general

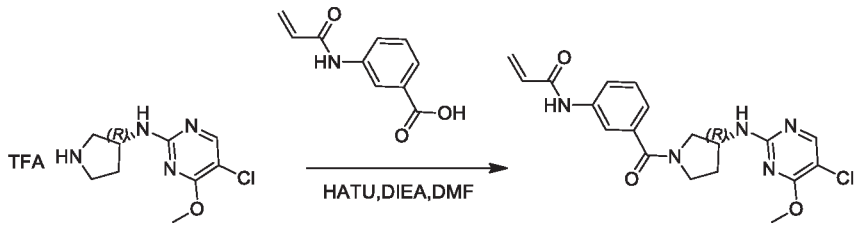
procedure of (R)-1-(6-(3-((5-chloro-4-methoxypyrimidin-2-yl)amino)pyrrolidine-1-carbonyl)-2-azaspiro[3.3]heptan-2-yl)prop-2-en-1-one. ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.87-2.27 (m, 4H), 3.35-3.38 (m, 1H), 3.44-3.79 (m, 4H), 3.85-3.93 (m, 3H), 4.23-4.41 (m, 1H), 5.05-5.10 (m, 1H), 5.76 (d, J = 10.4 Hz, 1H), 6.25 (d, J = 16.8 Hz, 1H), 6.68-6.76 (m, 1H), 7.08-7.14 (m, 2H), 7.82-7.85 (m, 1H), 8.10-8.16 (m, 1H), 8.32 (s, 1H), 8.39 (s, 1H), 9.22 (s, 0.5H), 9.24 (s, 0.5H). [M+H] Calc'd for $C_{22}H_{24}ClN_5O4$, 458.1; Found, 458.1.

Example 104: Synthesis of (R)-N-(4-(3-((5-bromopyrimidin-2-yl)amino)pyrrolidine-1-carbonyl)phenyl)-N-methylacrylamide

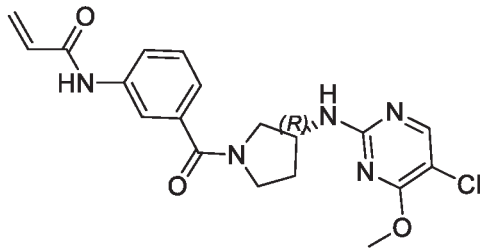


To a solution of 4-(N-methylacrylamido)benzoic acid (100 mg, 0.49 mmol), (R)-5-bromo-N-(pyrrolidin-3-yl)pyrimidin-2-amine, HCl salt (150 mg, 0.54 mmol) and DIEA (189 mg, 1.47 mmol) in DMF (15 mL) was added HATU (205 g, 0.54 mmol) at rt. The mixture was stirred at rt overnight. The mixture was diluted with water (20 mL) and extracted with EtOAc (20 mL*2). The combined organic layers were washed with water (20 mL*2), washed with brine (20 mL), dried over Na_2SO_4, filtered and concentrated. The residue was purified by *prep*-HPLC to afford (R)-N-(4-(3-((5-bromopyrimidin-2-yl)amino)pyrrolidine-1-carbonyl)phenyl)-N-methylacrylamide (35.3 mg, 17%). ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.86-2.01 (m, 1H), 2.11-2.19 (m, 1H), 3.26 (s, 1.5H), 3.28 (s, 1.5H), 3.33-3.80 (m, 4H), 4.26-4.43 (m, 1H), 5.60 (d, J = 10.4 Hz, 1H), 6.09-6.19 (m, 2H), 7.31-7.36 (m, 2H), 7.56-7.61 (m, 2H), 7.81-7.84 (m, 1H), 8.36 (s, 1H), 8.43 (s, 1H). [M+H] MS Calcd for $C_{19}H_{20}BrN_5O_2$: 430.1; MS Found: 430.1.

Example 105: Synthesis of (*R*)-*N*-(3-(3-((5-chloro-4-methoxypyrimidin-2-yl)amino)pyrrolidine-1-carbonyl)phenyl)acrylamide

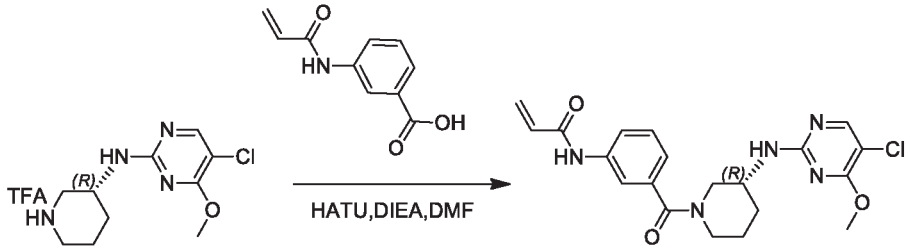


Step 1: (R)-N-(3-(3-((5-chloro-4-methoxypyrimidin-2-yl)amino)pyrrolidine-1-carbonyl)phenyl)acrylamide



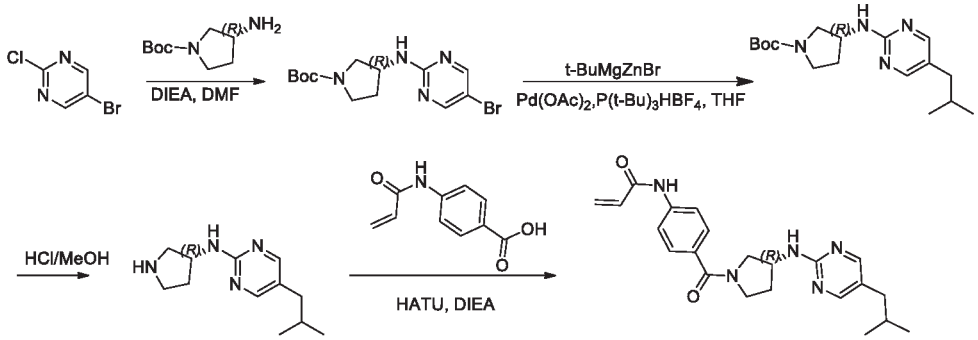
[00500] The title compound was prepared in 29% yield from (*R*)-5-chloro-4-methoxy-*N*-(pyrrolidin-3-yl)pyrimidin-2-amine 2,2,2-trifluoroacetate using general procedure of (*R*)-*N*-(4-(3-((5-chloro-4-methylpyrimidin-2-yl)amino)pyrrolidine-1-carbonyl)phenyl)acrylamide. ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.90-2.02 (m, 1H), 2.07-2.18 (m, 1H), 3.34-3.75 (m, 4H), 3.85 (s, 1.5H), 3.94 (s, 1.5H), 4.26-4.44 (m, 1H), 5.77 (d, J = 12.0 Hz, 1H), 6.23-6.29 (m, 1H), 6.38-6.46 (m, 1H), 7.18-7.23 (m, 1H), 7.34-7.41 (m, 1H), 7.61-7.72 (m, 2H), 7.89-7.92 (m, 1H), 8.06 (s, 0.5H), 8.14 (s, 0.5H), 10.23 (s, 0.5H), 10.26 (s, 0.5H). [M+H] Calc'd for $C_{19}H_{20}ClN_5O_3$, 402.1; Found, 402.1.

Example 106: Synthesis of (*R*)-*N*-(3-(3-((5-chloro-4-methoxypyrimidin-2-yl)amino)piperidine-1-carbonyl)phenyl)acrylamide

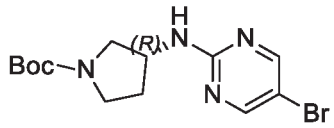


[00501] The title compound was prepared in 23% yield from (R)-5-chloro-4-methoxy-N-(piperidin-3-yl)pyrimidin-2-amine 2,2,2-trifluoroacetate using general procedure of (*R*)-*N*-(4-(3-((5-chloro-4-methylpyrimidin-2-yl)amino)pyrrolidine-1-carbonyl)phenyl)acrylamide. ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.49-1.85 (m, 2H), 1.91-2.07 (m, 2H), 2.66-3.02 (m, 1H), 3.21-3.24 (m, 1H), 3.37-3.58 (m, 3H), 3.80-3.94 (m, 3H), 5.75-5.78 (m, 1H), 6.26 (d, J = 16.8 Hz, 1H), 6.39-6.47 (m, 1H), 6.95-7.09 (m, 1H), 7.14-7.38 (m, 2H), 7.54-7.77 (m, 2H), 7.95-8.12 (m, 1H), 10.15 (br s, 0.6H), 10.25 (br s, 0.4H). [M+H] Calc'd for $C_{20}H_{22}ClN_5O_3$, 416.1; Found, 416.1.

Example 107: Synthesis of (*R*)-*N*-(4-(3-((5-isobutylpyrimidin-2-yl)amino)pyrrolidine-1-carbonyl)phenyl)acrylamide

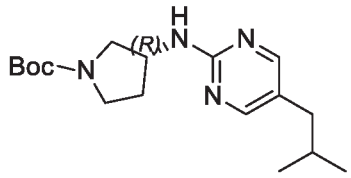


Step 1: (R)-tert-butyl 3-((5-bromopyrimidin-2-yl)amino)pyrrolidine-1-carboxylate



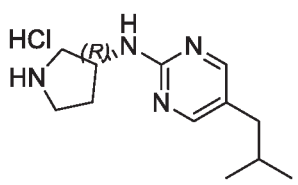
[00502] The title compound was prepared in 85% yield from 5-bromo-2-chloropyrimidine using general procedure of (*R*)-*tert*-butyl 3-((5-chloro-4-methylpyrimidin-2-yl)amino)pyrrolidine-1-carboxylate. [M+H] Calc'd for $C_{13}H_{19}BrN_4O_2$, 343.0; Found, 343.0

Step 2: (R)-tert-butyl 3-((5-isobutylpyrimidin-2-yl)amino)pyrrolidine-1-carboxylate



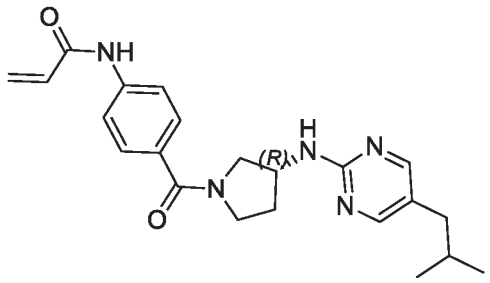
To a mixture of (R)-tert-butyl 3-((5-bromopyrimidin-2-yl)amino)pyrrolidine-1-carboxylate (100 mg, 0.29 mmol), $Pd(OAc)_2$ (13 mg, 0.06 mmol) and $P(t\text{-}Bu)_3HBF_4$ (33 mg, 0.12 mmol) in THF (3 mL) at 0°C was added t-BuZnBr (2.6 mL, 0.87 mmol, 0.33 M). The mixture was stirred at RT for 1 hour. The mixture was quenched with water (10 mL) and extracted with EtOAc (20 mL*2). The combined organic phase was concentrated. The residue was purified by flash chromatography on silica gel (petroleum ether/EtOAc = 5/1) to afford (*R*)-*tert*-butyl 3-((5-isobutylpyrimidin-2-yl)amino)pyrrolidine-1-carboxylate (60 mg, 65%) as a white solid. [M+H] Calc'd for $C_{17}H_{28}N_4O_2$, 321.2; Found, 321.2.

Step 3: (R)-5-isobutyl-N-(pyrrolidin-3-yl)pyrimidin-2-amine hydrochloride



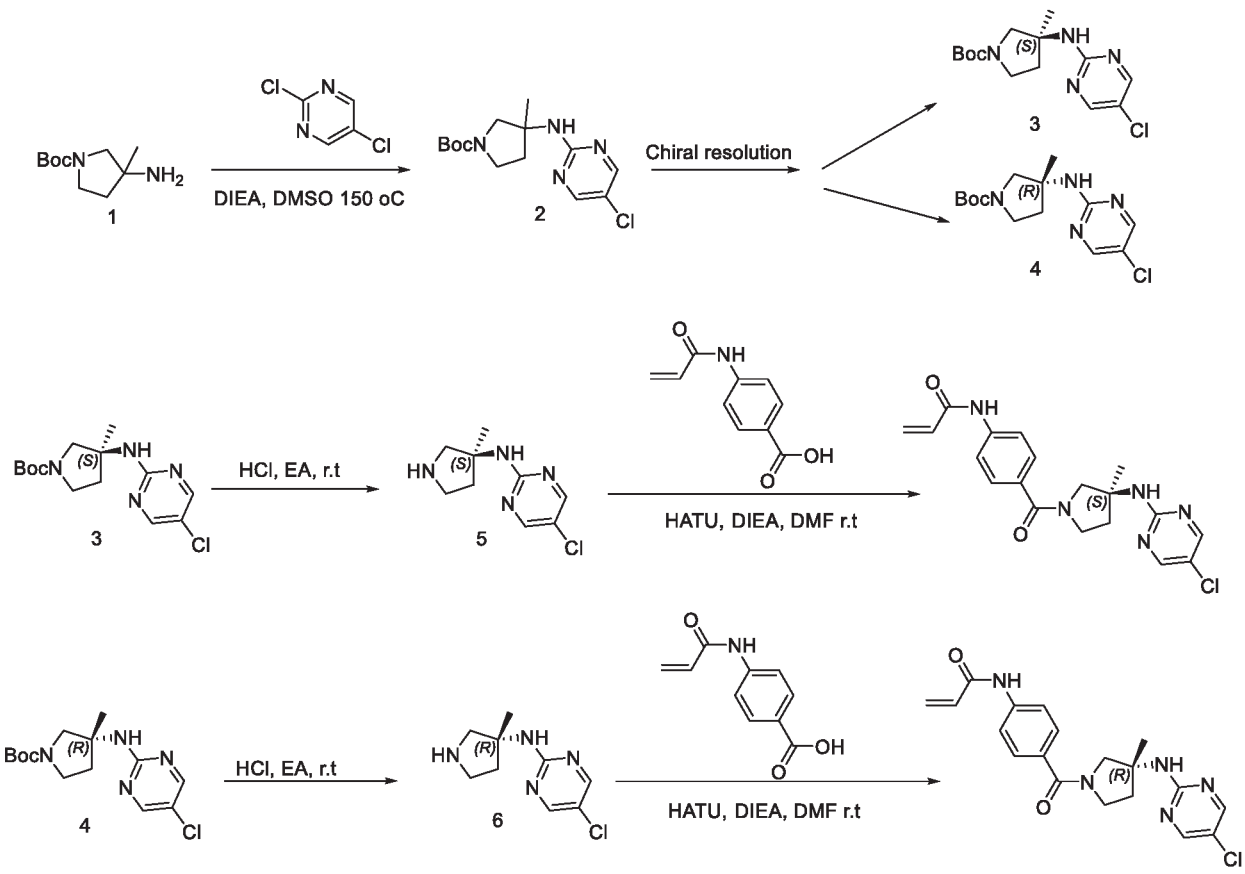
[00503] The title compound was prepared in 100% yield from (*R*)-*tert*-butyl 3-((5-isobutylpyrimidin-2-yl)amino)pyrrolidine-1-carboxylate using general procedure of (*R*)-5-chloro-4-methyl-*N*-(pyrrolidin-3-yl)pyridin-2-amine hydrochloride. [M+H] Calc'd for $C_{12}H_{20}N_4$, 221.1; Found, 221.1.

Step 4: (R)-N-(4-(3-((5-isobutylpyrimidin-2-yl)amino)pyrrolidine-1-carbonyl)phenyl)acrylamide

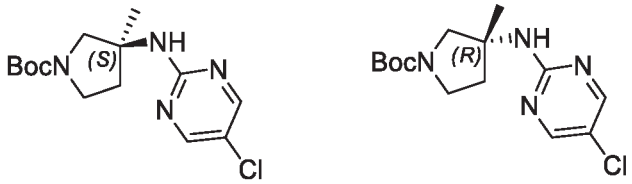


[00504] The title compound was prepared in 36% yield from (*R*)-5-isobutyl-*N*-(pyrrolidin-3-yl)pyrimidin-2-amine hydrochloride using general procedure of (*R*)-*N*-(4-(3-((5-chloro-4-methylpyrimidin-2-yl)amino)pyrrolidine-1-carbonyl)phenyl)acrylamide. ^{1}H NMR (400 MHz, DMSO-d_6): δ 0.73-0.86 (m, 6H), 1.67-1.75 (m, 1H), 1.86-2.09 (m, 1H), 2.14-2.27 (m, 3H), 3.33-3.35 (m, 1H), 3.40-3.51(m, 1H), 3.56-3.69 (m, 1H), 3.73-3.79 (m, 1H), 4.23-4.42 (m, 1H), 5.78 (d, *J* = 10.0 Hz, 1H), 6.27 (d, *J* = 16.8 Hz, 1H), 6.40-6.48 (m, 1H), 7.29-7.33 (m, 1H), 7.48-7.54 (m, 2H), 7.68-7.73 (m, 2H), 8.07 (s, 1H), 8.14 (s, 1H), 10.31 (br s, 1H). [M+H] Calc'd for $C_{22}H_{27}N_5O_2$, 394.2 ; Found, 394.2.

Example 108 & 109: (S)-N-(4-(3-((5-chloropyrimidin-2-yl)amino)-3-methylpyrrolidine-1-carbonyl)phenyl)acrylamide&(R)-N-(4-(3-((5-chloropyrimidin-2-yl)amino)-3-methylpyrrolidine-1-carbonyl)phenyl)acrylamide

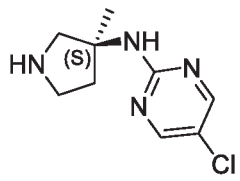


Step 1: (S)-tert-butyl 3-((5-chloropyrimidin-2-yl)amino)-3-methylpyrrolidine-1-carboxylate & (R)-tert-butyl 3-((5-chloropyrimidin-2-yl)amino)-3-methylpyrrolidine-1-carboxylate



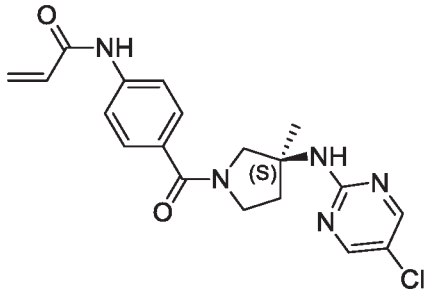
[00505] To a solution of tert-butyl 3-amino-3-methylpyrrolidine-1-carboxylate (460 mg, 2.3 mmol) and 2,5-dichloropyrimidine (1.7 g, 11.5 mmol) in DMSO (15 mL) was added DIEA (1.4 g, 11.5mmol) The mixture was stirred at 150°C for 1h. The mixture was cooled, diluted with water (200 mL) and extracted with EA (100 mL). The combined organic layer was washed with brine (100 mL), dried over Na_2SO_4 and concentrated *in vacuo*. The residue was purified by coclumn chromatography (PE:EA from 10:1 to 4:1) to afford 170 mg product as a white solid.Then Chiral separation (IG: Hex:EtOH = 80:20) to get (S)-tert-butyl 3-((5-chloropyrimidin-2-yl)amino)-3-methylpyrrolidine-1-carboxylate (50 mg, 11.111 min) and (R)-tert-butyl3-((5-chloropyrimidin-2-yl)amino)-3-methylpyrrolidine-1-carboxylate (50 mg, 13.614 min). [M+H] Calc'd for $C_9H_{13}ClN_4$, 313.1; Found, 313.1.

Step 2: (S)-tert-butyl 3-((5-chloropyrimidin-2-yl)amino)-3-methylpyrrolidine-1-carboxylate



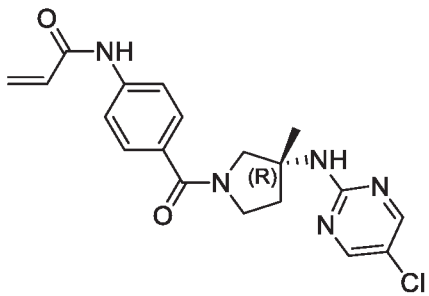
[00506] To a solution of (S)-tert-butyl 3-((5-chloropyrimidin-2-yl)amino)-3-methylpyrrolidine-1-carboxylate (50 mg, 0.16 mmol) in EA (10 mL) was added HCl (gas) at -50°C. The reaction mixture was stirred at rt for 3 h. The reaction mixture was concentrated to afford 50 mg crude product as a yellow solid. [M+H] Calc'd for $C_9H_{13}ClN_4$, 213.1; Found, 213.1.

Step 3: (S)-N-(4-(3-((5-chloropyrimidin-2-yl)amino)-3-methylpyrrolidine-1-carbonyl)phenyl)acrylamide



[00507] To a solution of (S)-tert-butyl 3-((5-chloropyrimidin-2-yl)amino)-3-methylpyrrolidine-1-carboxylate (50 mg, 0.23 mmol) and 4-acrylamidobenzoic acid (44 mg, 0.23 mmol) in DMF (3 mL) was added HATU (105 mg, 0.27 mmol) and DIEA (90 mg, 0.69 mmol) at RT. The mixture was stirred at rt for 2h, The reaction mixture was concentrated *in vacuo*. The residue was purified by prep-HPLC to afford (R)-N-(4-(3-((5-cyanopyrimidin-2-yl)amino)pyrrolidine-1-carbonyl)-2-(2-(dimethylamino)ethoxy)phenyl)acrylamide (25.4 mg, 25.4%) as a white solid. ^{1}H NMR (400 MHz, CD_3OD): δ 1.50 (s, 2H), 1.63 (s, 1H), 2.07-2.13 (m, 1H), 2.46-2.49 (m, 1H), 3.61-3.82 (m, 3H), 4.16-4.19 (d, J = 11.2 Hz, 1H), 5.79-5.83 (m, 1H), 6.37-6.45 (m, 2H), 7.44-7.56 (m, 2H), 7.71-7.87 (m, 2H), 8.19 (s, 1H), 8.30 (s, 1H). [M+H] Calc'd for $C_{19}H_{20}ClN_5O_2$, 386.1; Found,386.1.

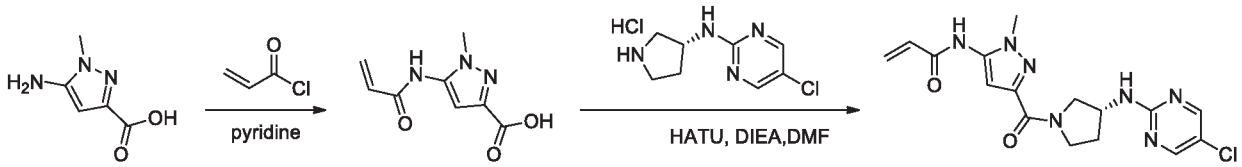
Step 4: (R)-N-(4-(3-((5-cyanopyrimidin-2-yl)amino)pyrrolidine-1-carbonyl)-2-(2-(dimethylamino)ethoxy)phenyl)acrylamide



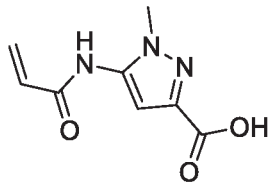
[00508] To a solution of (R)-5-chloro-N-(3-methylpyrrolidin-3-yl)pyrimidin-2-amine (50 mg, 0.23 mmol) and 4-acrylamidobenzoic acid (44 mg, 0.23 mmol) in DMF (3 mL) was added HATU (105 mg,

0.27 mmol) and DIEA (90 mg, 0.69 mmol). Tthe reaction mixture was stirred at RT for 2h. The reaction mixture was concentrated. The residue was purified by *prep*-HPLC to afford (R)-N-(4-(3-((5-cyanopyrimidin-2-yl)amino)pyrrolidine-1-carbonyl)-2-(2-(dimethylamino)ethoxy)phenyl)acrylamide (37.7 mg, 31%) as a white solid. ^{1}H NMR (400 MHz, CD_3OD): δ 1.50 (s, 2H), 1.63 (s, 1H), 2.07-2.13 (m, 1H), 2.46-2.49 (m, 1H), 3.61-3.82 (m, 3H), 4.16-4.19 (d, J = 11.2 Hz, 1H), 5.79-5.83 (m, 1H), 6.37-6.45 (m, 2H), 7.44-7.56 (m, 2H), 7.71-7.87 (m, 2H), 8.19 (s, 1H), 8.30 (s, 1H). [M+H] Calc'd for $C_{19}H_{20}ClN_5O_2$, 386.1; Found,386.1.

Example 110: Synthesis of (*R*)-*N*-(3-(3-((5-chloropyrimidin-2-yl)amino)pyrrolidine-1-carbonyl)-1-methyl-1*H*-pyrazol-5-yl)acrylamide

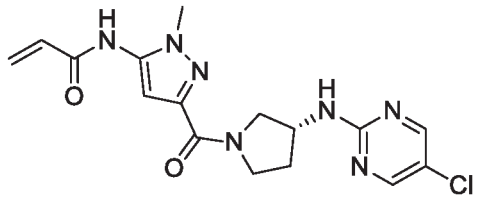


Step 1: 5-acrylamido-1-methyl-1H-pyrazole-3-carboxylic acid



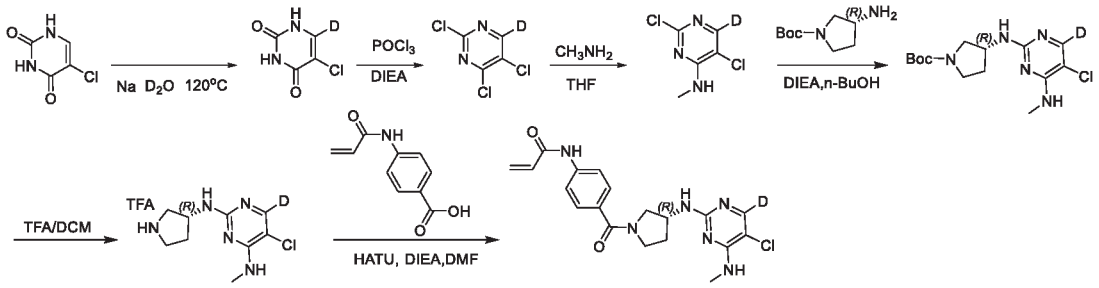
[00509] The title compound (crude) was prepared in 100% yield from 5-amino-1-methyl-1*H*-pyrazole-3-carboxylic acid using general procedure of 4-acrylamido-3-methylbenzoic acid. [M+H] Calc'd for $C_8H_9N_3O_3$, 196.1; Found, 196.1.

Step 2: (R)-N-(3-(3-((5-chloropyrimidin-2-yl)amino)pyrrolidine-1-carbonyl)-1-methyl-1H-pyrazol-5-yl)acrylamide

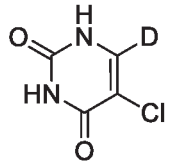


[00510] The title compound was prepared in 20% yield from 5-acrylamido-1-methyl-1H-pyrazole-3-carboxylic acid using general procedure of (*R*)-*N*-(4-(3-((5-chloro-4-methylpyrimidin-2-yl)amino)pyrrolidine-1-carbonyl)phenyl)acrylamide. ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.89-1.98 (m, 1H), 2.09-2.21 (m, 1H), 3.44-3.56 (m, 1H), 3.64-3.69 (m, 0.5H), 3.72-3.77 (m, 4H), 3.91-3.96 (m, 0.5H), 4.00-4.14 (m, 1H), 4.29-4.40 (m, 1H), 5.82-5.85 (m, 1H), 6.28-6.33 (m, 1H), 6.46-6.54 (m, 1H), 6.64 (s, 0.5H), 6.65 (s, 0.5H), 7.78-7.80 (m, 1H), 8.36 (s, 1H), 8.38 (s, 1H), 10.31 (br s, 1H). [M+H] Calc'd for $C_{16}H_{18}ClN_7O_2$, 376.1; Found, 376.1.

Example 111: Synthesis of(R)-N-(4-(3-((5-chloro-4-deutero-6-(methylamino)pyrimidin-2-yl)amino)pyrrolidine-1-carbonyl)phenyl)acrylamide

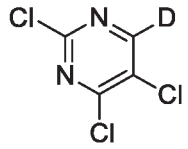


Step 1: 5-chloro-6-deuteropyrimidine-2,4(1H,3H)-dione



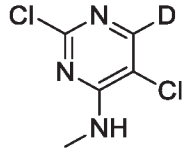
[00511] Na (1.0 g, 4.3 mmol) was added to D_2O (5 mL) at 0°C. The mixture was used directly in the next step. A mixture of 5-chloropyrimidine-2,4(1*H*,3*H*)-dione (2.0 g, 13.7 mmol) and NaOD (1.7 g, 41.1 mmol) in D_2O (6 mL) was stirred at 120°C under N_2 overnight. The mixture was cooled to RT and filtered. The filter cake was dried to afford 5-chloro-6-deuteropyrimidine-2,4(1H,3H)-dione (1.5 g, 75%) as a yellow solid. [M+H] Calc'd for $C_4H_2DClN_2O_2$, 147.9; Found, 147.9.

Step 2: 2,4,5-trichloro-6-deuteropyrimidine



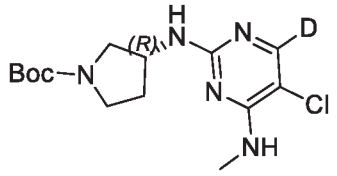
[00512] A mixture of5-chloro-6-deuteropyrimidine-2,4(1H,3H)-dione (240 mg, 1.6 mmol) and DIEA (413 mg, 3.2 mmol) in $POCl_3$ (2.5 g, 16.3 mmol) was stirred at 110°C for 24 h. The solution was cooled to RT and added to hot water dropwise. Then the reaction mixture was extracted with DCM (30 mL*2). The combined organic phase was concentrated *in vacuo* to afford 2,4,5-trichloro-6-deuteropyrimidine (360 mg, crude, 100%) as yellow oil. [M+H] Calc'd for $C_4DCl_3N_2$, 183.9; Found, 183.9.

Step 3: 2,5-dichloro-6-deutero-N-methylpyrimidin-4-amine



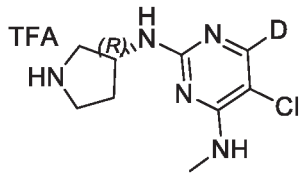
[00513] The title compound was prepared in 58% yield from2,4,5-trichloro-6-deuteropyrimidine using general procedure of 2,5-dichloro-*N*,*N*-dimethylpyrimidin-4-amine. [M+H] Calc'd for $C_5H_4DCl_2N_3$, 178.9; Found, 178.9

Step 4: (R)-tert-butyl 3-((5-chloro-4-deutero-6-(methylamino)pyrimidin-2-yl)amino)pyrrolidine-1-carboxylate



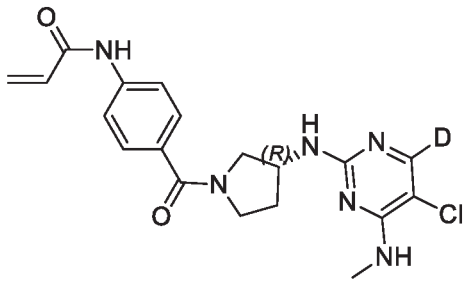
[00514] The title compound was prepared in 50% yield from 2,5-dichloro-6-deutero-N-methylpyrimidin-4-amine using general procedure of (*R*)-*tert*-butyl 3-((5-chloro-4-methylpyrimidin-2-yl)amino)pyrrolidine-1-carboxylate. [M+H] Calc'd for $C_{14}H_{21}DClN_5O_2$, 329.1; Found, 329.1.

Step 5: (R)-5-chloro-6-deutero-N4-methyl-N2-(pyrrolidin-3-yl)pyrimidine-2,4-diamine 2,2,2-trifluoroacetate



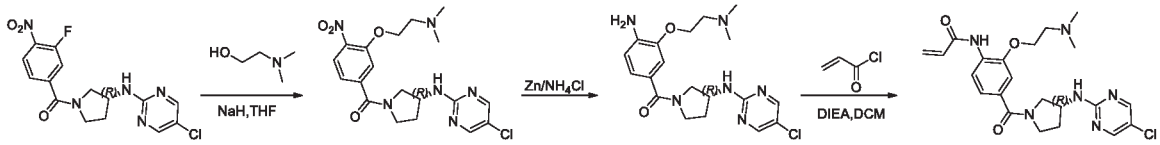
[00515] The title compound was prepared in 100% yield from(R)-tert-butyl 3-((5-chloro-4-deutero-6-(methylamino)pyrimidin-2-yl)amino)pyrrolidine-1-carboxylate using general procedure of (*R*)-5-chloro-4-methyl-N-(pyrrolidin-3-yl)pyrimidin-2-amine 2,2,2-trifluoroacetate. [M+H] Calc'd for $C_9H_{13}DClN_5$, 229.1; Found, 229.1.

Step 6: (R)-N-(4-(3-((5-chloro-4-deutero-6-(methylamino)pyrimidin-2-yl)amino)pyrrolidine-1-carbonyl)phenyl)acrylamide

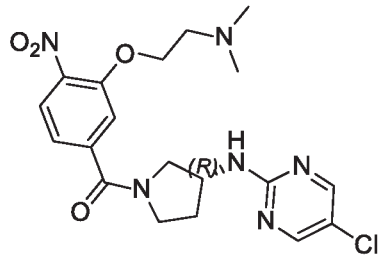


[00516] The title compound was prepared in 31% yield from (R)-5-chloro-6-deutero-N4-methyl-N2-(pyrrolidin-3-yl)pyrimidine-2,4-diamine 2,2,2-trifluoroacetate using general procedure of (*R*)-*N*-(4-(3-((5-chloro-4-methylpyrimidin-2-yl)amino)pyrrolidine-1-carbonyl)phenyl)acrylamide. ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.96-1.99 (m, 1H), 2.09-2.13 (m, 1H), 2.74 (s, 1.5H), 2.85 (s, 1.5H), 3.42-3.77 (m, 4H), 4.21-4.38 (m, 1H), 5.76-5.79 (m, 1H), 6.28 (d, J = 16.8 Hz, 1H), 6.41-6.48 (m, 1H), 6.88-6.92 (m, 1H), 7.02 (br s, 1H), 7.48-7.53 (m, 2H), 7.69-7.73 (m, 2H), 10.30 (s, 1H). [M+H] Calc'd for $C_{19}H_{20}DClN_6O_2$, 402.1; Found, 402.1.

Example 112: Synthesis of (*R*)-*N*-(4-(3-((5-chloropyrimidin-2-yl)amino)pyrrolidine-1-carbonyl)-2-(2-(dimethylamino)ethoxy)phenyl)acrylamide

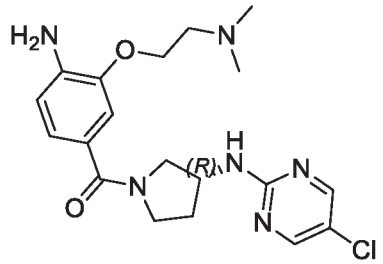


Step 1: (R)-(3-((5-chloropyrimidin-2-yl)amino)pyrrolidin-1-yl)(3-(2-(dimethylamino)ethoxy)-4-nitrophenyl)methanone



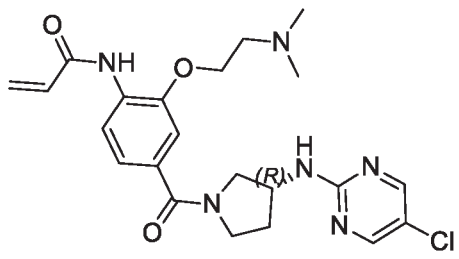
[00517] The title compound was prepared in 100% yield from (*R*)-(3-((5-chloropyrimidin-2-yl)amino)pyrrolidin-1-yl)(3-fluoro-4-nitrophenyl)methanone using general procedure of ((R)-3-((5-chloropyrimidin-2-yl)amino)pyrrolidin-1-yl)(4-nitro-3-((tetrahydrofuran-3-yl)oxy)phenyl)methanone. [M+H] Calc'd for $C_{19}H_{23}ClN_6O_4$, 435.1; Found, 435.1.

Step 2: (R)-(4-amino-3-(2-(dimethylamino)ethoxy)phenyl)(3-((5-chloropyrimidin-2-yl)amino)pyrrolidin-1-yl)methanone



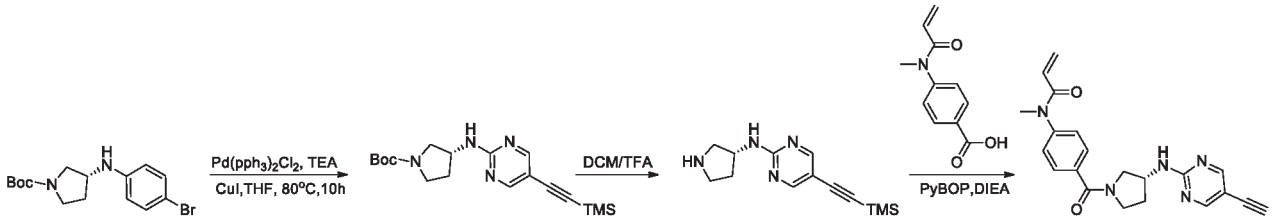
[00518] The title compound was prepared in 80% yield from (R)-(3-((5-chloropyrimidin-2-yl)amino)pyrrolidin-1-yl)(3-(2-(dimethylamino)ethoxy)-4-nitrophenyl)methanone using general procedure of (4-amino-3-((tetrahydrofuran-3-yl)oxy)phenyl)((R)-3-((5-chloropyrimidin-2-yl)amino)pyrrolidin-1-yl)methanone. [M+H] Calc'd for $C_{19}H_{25}ClN_6O_2$, 405.1; Found, 405.1.

Step 3: (R)-N-(4-(3-((5-chloropyrimidin-2-yl)amino)pyrrolidine-1-carbonyl)-2-(2-(dimethylamino)ethoxy)phenyl)acrylamide

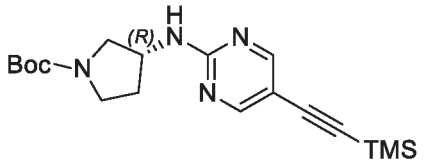


[00519] The title compound was prepared in 18% yield from (R)-(4-amino-3-(2-(dimethylamino)ethoxy)phenyl)(3-((5-chloropyrimidin-2-yl)amino)pyrrolidin-1-yl)methanone using general procedure of (R)-1-(6-(3-((5-chloro-4-methoxypyrimidin-2-yl)amino)pyrrolidine-1-carbonyl)-2-azaspiro[3.3]heptan-2-yl)prop-2-en-1-one. ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.87-2.01 (m, 1H), 3.10-2.19 (m, 1H), 2.22 (s, 3H), 2.24 (s, 3H), 2.60-2.64 (m, 2H), 3.41-3.44 (m, 1H), 3.52-3.57 (m, 1H), 3.64-3.67 (m, 1H), 3.74-3.80 (m, 1H), 4.12-4.18 (m, 2H), 4.22-4.41 (m, 1H), 5.78 (d, J = 10.0 Hz, 1H), 6.26 (d, J = 16.8 Hz, 1H), 6.52-6.59 (m, 1H), 7.12-7.18 (m, 1H), 7.23 (s, 0.5H), 7.27 (s, 0.5H), 7.83 (br s, 1H), 8.12-8.17 (m, 1H), 8.32 (s, 1H), 8.39 (s, 1H), 9.67 (s, 0.5H), 9.71 (s, 0.5H). [M+H] Calc'd for $C_{22}H_{27}ClN_6O_3$, 459.1; Found, 459.1.

Example 113: Synthesis of (R)-N-(4-(3-((5-ethynylpyrimidin-2-yl)amino)pyrrolidine-1-carbonyl)phenyl)-N-methylacrylamide

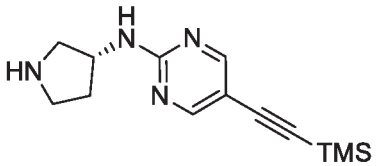


Step 1:(R)-tert-butyl3-((5-((trimethylsilyl)ethynyl)pyrimidin-2-yl)amino)pyrrolidine-1-carboxylate



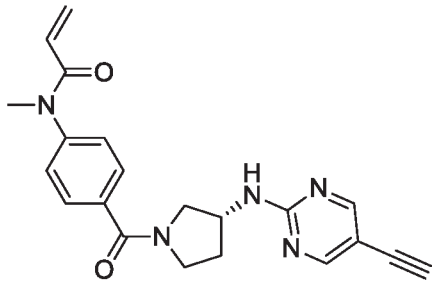
[00520] A solution of (R)-tert-butyl 3-((4-bromophenyl)amino)pyrrolidine-1-carboxylate (11.0 g, 32.2 mmmol), ethynyl trimethylsilane (12.6 g, 130.0 mmol), CuI (1.8 g, 9.7 mmol) and $Pd(PPh_3)_2Cl_2$ (2.3 g, 3.2 mmol) in TEA (80 mL) was stirred at 80 °C for 2h under N_2. The reaction mixture was cooled, diluted with water (150 mL) and extracted with EA (200 mL*2). The combined organic layers were washed with brine (150 mL), dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (PE/EA = 5/1) to give (R)-tert-butyl 3-((5-((trimethylsilyl)ethynyl)pyrimidin-2-yl)amino)pyrrolidine-1-carboxylate (9.2 g, 79%). [M+H] MS Calc'd $C_{18}H_{28}N_4O_2Si$: 361.2; Found: 361.2.

Step 2: (R)-N-(pyrrolidin-3-yl)-5-((trimethylsilyl)ethynyl)pyrimidin-2-amine



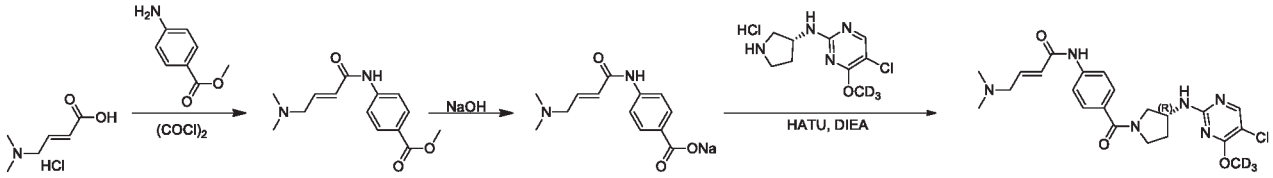
[00521] To a solution of (R)-tert-butyl 3-((5-((trimethylsilyl)ethynyl)pyrimidin-2-yl)amino)pyrrolidine-1-carboxylate (400 mg, 1.11 mmol) in DCM (8 mL) was added TFA (8 mL) at rt. DCM (20 mL) was added to the crude product and the reaction mixture was washed with sodium carbonate aqueous solution. The organics were dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure to give (R)-N-(pyrrolidin-3-yl)-5-((trimethylsilyl)ethynyl)pyrimidin-2-amine (220 mg, 76%) as a brown solid. [M+H] MS Calc'd for $C_{13}H_{20}N_4Si$: 261.1; Found: 261.1.

Step 3: (R)-N-(4-(3-((5-ethynylpyrimidin-2-yl)amino)pyrrolidine-1-carbonyl)phenyl)-N-methylacrylamide

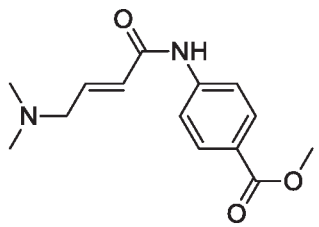


[00522] A mixture of 4-(N-methylacrylamido)benzoic acid (118 mg, 0.57 mmol), (R)-N-(pyrrolidin-3-yl)-5-((trimethylsilyl)ethynyl)pyrimidin-2-amine (120 mg, 0.64 mmol), PyBOP (332 mg, 6.38 mmol) and DIEA (412 mg, 3.19 mmol) in DMF (10 mL) was stirred at rt 3 h. The reaction mixture was concentrated. The residue was purified by *prep*-HPLC to (R)-N-(4-(3-((5-ethynylpyrimidin-2-yl)amino)pyrrolidine-1-carbonyl)phenyl)acrylamide (108.4 mg, 33.9%) as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6): 1.89-1.99 (m, 1H), 2.14-2.17 (m, 1H), 3.26 (s, 1.5H), 3.29 (s, 1.5H), 3.48-3.78 (m, 4H), 4.24-4.26 (m, 1H), 4.33-4.48 (m, 1H), 5.60 (d, J = 7.2 Hz, 1H), 6.14-6.16 (m, 2H), 7.31-7.36 (m, 2H), 7.56-7.61 (m, 2H), 8.01 (t, J = 9.2 Hz, 1H), 8.39 (s, 1H), 8.45 (s, 1H). [M+H] Calc'd for $C_{21}H_{21}N_5O_2$: 376.2; Found: 376.2.

Example 114: Synthesis of(R,E)-N-(4-(3-((5-chloro-4-(trideuteromethoxy)pyrimidin-2-yl)amino)pyrrolidine-1-carbonyl)phenyl)-4-(dimethylamino)but-2-enamide

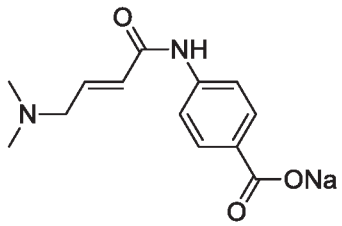


Step 1: (E)-methyl 4-(4-(dimethylamino)but-2-enamido)benzoate



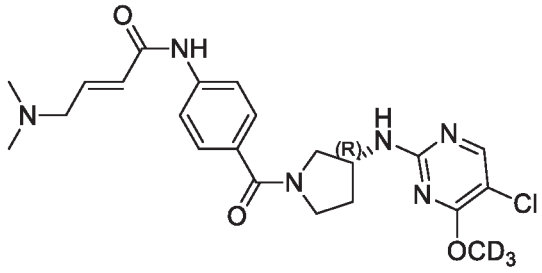
[00523] To a solution of (*E*)-4-(dimethylamino)but-2-enoic acid hydrochloride (1.0 g, 6.0 mmol) in DCM/DMF (15 mL/ 2 drops) was added oxalyl chloride (1.5 g, 11.8 mmol) dropwise at 0°C under N_2. The solution was stirred at RT for 2 hours. The mixure was concentrated at 30°C. The residue was dissolved in THF (10 mL) and was added to a mixture of methyl 4-aminobenzoate (453 mg, 3.0 mmol) and DIEA (2.3 g, 18 mmol) in THF (10 mL) at 0°C. The solution was stirred at RT for 2 hours. The solution was concentrated and the residue was diluted with DCM (50 mL), washed with brine (20*3 mL), dried over Na_2SO_4 and filtered. The filtrate was concentrated *in vacuo* and the residue was purified by flash chromatography on silica gel (DCM/MeOH = 20/1) to afford (*E*)-methyl 4-(4-(dimethylamino)but-2-enamido)benzoate (340 mg, 21%) as a brown solid. [M+H] Calc'd for $C_{14}H_{18}N_2O_3$, 263.1; Found, 263.1.

Step 2: sodium (E)-4-(4-(dimethylamino)but-2-enamido)benzoate



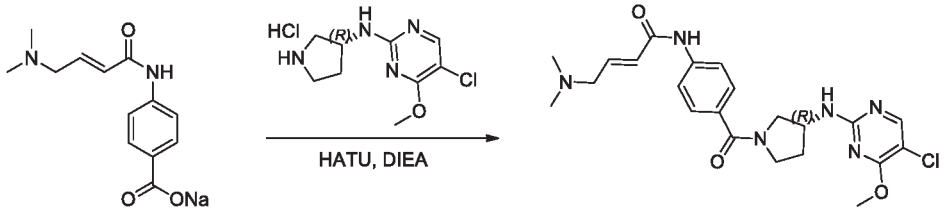
[00524] A mixture of (E)-methyl 4-(4-(dimethylamino)but-2-enamido)benzoate (340 mg, 1.3 mmol) in THF/H_2O (3 mL/ 3 mL) was stirred at 65°C for 5 hours. The solution was concentrated to afford sodium (*E*)-4-(4-(dimethylamino)but-2-enamido)benzoate (307 mg, 87%) as a yellow solid. [M+H-22] Calc'd for $C_{13}H_{15}N_2NaO_3$, 249.1; Found, 249.1.

Step 3: (R,E)-N-(4-(3-((5-chloro-4-(trideuteromethoxy)pyrimidin-2-yl)amino)pyrrolidine-1-carbonyl)phenyl)-4-(dimethylamino)but-2-enamide



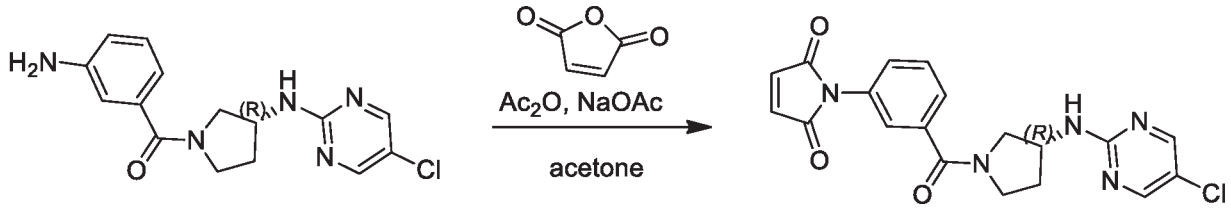
[00525] The title compound was prepared in 15% yield from sodium (*E*)-4-(4-(dimethylamino)but-2-enamido)benzoate using general procedure of (*R*)-*N*-(4-(3-((5-chloro-4-methylpyrimidin-2-yl)amino)pyrrolidine-1-carbonyl)phenyl)acrylamide. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.95-2.01 (m, 1H), 2.27 (s, 6H), 2.29-2.38 (m, 1H), 3.10 (d, *J* = 5.6 Hz, 2H), 3.39-3.42 (m, 0.5H), 3.60-3.90 (m, 3H), 3.99-4.03 (m, 0.5H), 4.42-4.54 (m, 1H), 5.15-5.26 (m, 1H), 6.14 (d, *J* = 15.2 Hz, 1H), 6.94-7.00 (m, 1H), 7.45-7.50 (m, 2H), 7.56-7.60 (m, 2H), 7.82-7.85 (m, 1H), 7.96-8.03 (m, 1H). [M+H] Calc'd for $C_{22}H_{24}D_3ClN_6O_3$, 462.2; Found, 462.2.

Example 115: Synthesis of (*R*,*E*)-*N*-(4-(3-((5-chloro-4-methoxypyrimidin-2-yl)amino)pyrrolidine-1-carbonyl)phenyl)-4-(dimethylamino)but-2-enamide



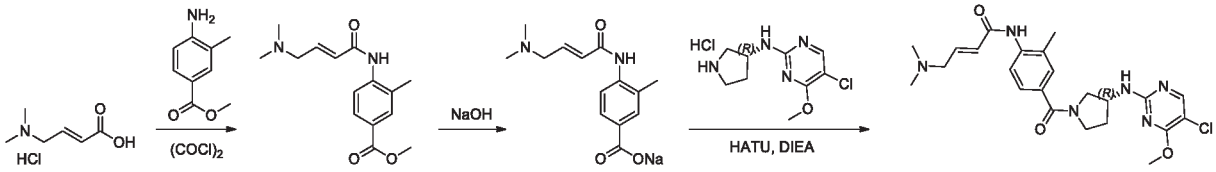
[00526] The title compound was prepared in 11% yield from sodium (*E*)-4-(4-(dimethylamino)but-2-enamido)benzoate using general procedure of (*R*)-*N*-(4-(3-((5-chloro-4-methylpyrimidin-2-yl)amino)pyrrolidine-1-carbonyl)phenyl)acrylamide. ^{1}H NMR (400 MHz, DMSO-d_6): δ 2.00-2.07 (m, 1H), 2.14-2.19 (m, 7H), 3.06 (d, J = 5.2 Hz, 2H), 3.35-3.38 (m, 1H), 3.40-3.45 (m, 1H), 3.61-3.65 (m, 1H), 3.75-3.78 (m, 1H), 3.85 (s, 1.5H), 3.94 (s, 1.5H), 4.22-4.45 (m, 1H), 6.27 (d, J = 15.2 Hz, 1H), 6.72-6.77 (m, 1H), 7.47-7.52 (m, 2H), 7.67-7.71 (m, 3H), 8.07 (s, 0.5H), 8.14 (s, 0.5H), 10.20 (s, 1H). [M+H] Calc'd for $C_{22}H_{27}ClN_6O_3$, 459.1; Found, 459.1.

Example 116: Synthesis of (R)-1-(3-(3-((5-chloropyrimidin-2-yl)amino)pyrrolidine -1-carbonyl)phenyl)-1H-pyrrole-2,5-dionefuran-2,5-dione

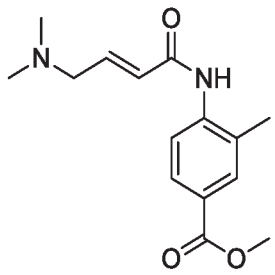


[00527] A mixture of (R)-(3-aminophenyl)(3-((5-chloropyrimidin-2-yl)amino)Pyrrolidin-1-yl)methanone(175 mg, 0.55 mmol) and furan-2,5-dione (81.5 mg, 0.83 mmol) in acetone (5 mL) was stirred at 20 °C for 2 hrs. The reaction mixture was concentrated. To the residue was added a solution of sodium acetate (45 mg, 0.55 mmol) and acetic anhydride (112 mg, 1.1 mmol) in DMF(3 mL). The mixture was stirred at 50°C for 5 hrs. The mixture was cooled, filtered and concentrated. The residue was purified by silica gel chromatography (DCM/MeOH = 20/1) to afford (R)-1-(3-(3-((5-chloropyrimidin-2-yl)amino)pyrrolidine-1-carbonyl)phenyl)-1H-pyrrole-2,5-dionefuran-2,5-dione (91.0 mg, 41%) as a yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$): 2.00-2.03 (m, 1H), 2.27-2.27 (m, 1H), 3.40-3.62 (m, 2H), 3.63-4.03 (m, 2H), 4.47-4.57 (m, 1H), 5.28-5.36 (m, 1H), 6.86-6.88 (m, 2H), 7.44-7.57 (m, 4H), 8.19 (s, 1H), 8.25 (s, 1H). [M+H] Calc'd for $C_{19}H_{16}ClN_5O_3$, 398.1; Found, 398.1.

Example 117: Synthesis of (*R*,*E*)-*N*-(4-(3-((5-chloro-4-methoxypyrimidin-2-yl)amino)pyrrolidine-1-carbonyl)-2-methylphenyl)-4-(dimethylamino)but-2-enamide

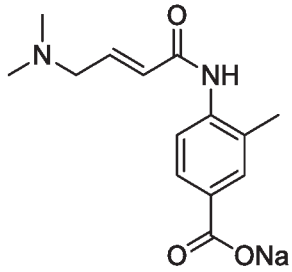


Step 1: (E)-methyl 4-(4-(dimethylamino)but-2-enamido)-3-methylbenzoate



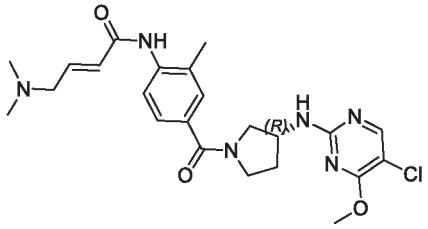
[00528] The title compound was prepared in 3.6% yield from (E)-4-(dimethylamino)but-2-enoic acid hydrochloride using general procedure of (*E*)-methyl 4-(4-(dimethylamino)but-2-enamido)benzoate. [M+H] Calc'd for $C_{15}H_{20}N_2O_3$, 277.1; Found, 277.1.

Step 2: sodium (E)-4-(4-(dimethylamino)but-2-enamido)-3-methylbenzoate



[00529] The title compound was prepared in 100% yield from (*E*)-methyl 4-(4-(dimethylamino)but-2-enamido)-3-methylbenzoate using general procedure of sodium (*E*)-4-(4-(dimethylamino)but-2-enamido)benzoate. [M+H-22] Calc'd for $C_{14}H_{17}N_2NaO_3$, 263.1; Found, 263.1.

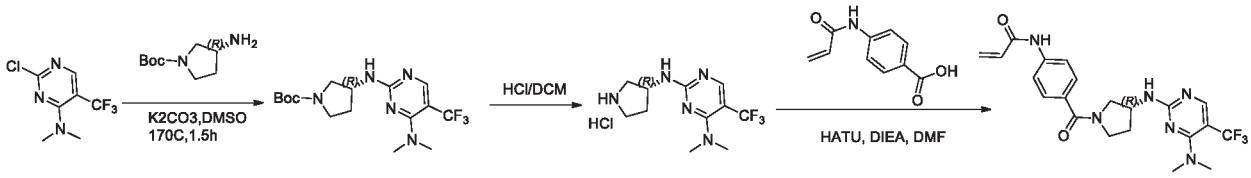
Step 3: (R,E)-N-(4-(3-((5-chloro-4-methoxypyrimidin-2-yl)amino)pyrrolidine-1-carbonyl)-2-methylphenyl)-4-(dimethylamino)but-2-enamide



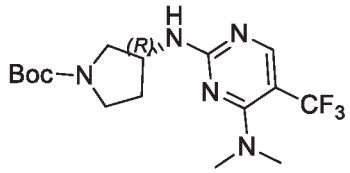
[00530] The title compound was prepared in 12% yield from sodium (E)-4-(4-(dimethylamino)but-2-enamido)-3-methylbenzoate using general procedure of (*R*)-*N*-(4-(3-((5-chloro-4-methylpyrimidin-2-yl)amino)pyrrolidine-1-carbonyl)phenyl)acrylamide. ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.89-2.01 (m, 1H), 2.14-2.19 (m, 7H), 2.22 (s, 1.5H), 2.25 (s, 1.5H), 3.06 (d, J = 6.0 Hz, 2H), 3.37-3.45 (m, 1H), 3.51-3.54 (m, 1H), 3.62-3.67 (m, 1H), 3.76-3.79 (m, 1H), 3.85 (s, 1.5H), 3.94 (s, 1.5H),

4.24-4.43 (m, 1H), 6.41 (d, J = 15.2 Hz, 1H), 6.70-6.77 (m, 1H), 7.30-7.39 (m, 2H), 7.61-7.66 (m, 2H), 8.07 (s, 0.5H), 8.14 (s, 0.5H), 9.40 (s, 1H). [M+H] Calc'd for $C_{23}H_{29}ClN_6O_3$, 473.1; Found, 473.1.

Example 118: (R)-N-(4-(3-((4-(dimethylamino)-5-(trifluoromethyl)pyrimidin-2-yl)amino)pyrrolidine-1-carbonyl)phenyl)acrylamide

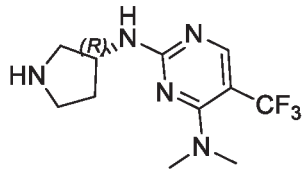


Step 1: (R)-tert-butyl 3-((4-(dimethylamino)-5-(trifluoromethyl)pyrimidin-2-yl)amino)pyrrolidine-1-carboxylate



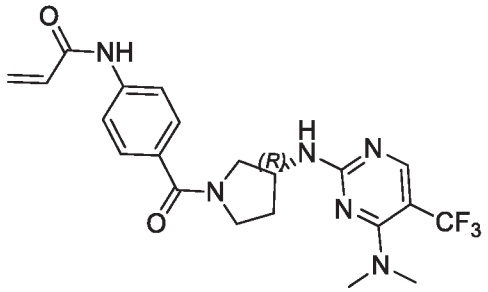
[00531] A mixture of 2-chloro-N,N-dimethyl-5-(trifluoromethyl)pyrimidin-4-amine (300 mg, 1.33 mmol), (R)-tert-butyl 3-aminopyrrolidine-1-carboxylate (298 mg, 1.60 mmol) and K_2CO_3 (276 mg, 2.00 mmol) in DMSO (3 mL) was stirred at 170°C for 1.5 h under microwave conditions. The reaction mixture was cooled, added H_2O (20 mL) and extracted with EA (20 mL*2). The combined organic layer was dried over Na_2SO_4, filtered and concentrated. The residue was purified by silica gel chromatography (PE/EA = 50/1 ~ 10/1) to afford (R)-tert-butyl 3-((4-(dimethylamino)-5-(trifluoromethyl)pyrimidin-2-yl)amino)pyrrolidine-1-carboxylate (350 mg, 70%) as a white solid. [M+H] Calc'd for $C_{16}H_{24}F_3N_5O_2$, 376.2; Found, 376.2.

Step 2: (R)-N4,N4-dimethyl-N2-(pyrrolidin-3-yl)-5-(trifluoromethyl)pyrimidine-2,4-diamine (HCl salt)



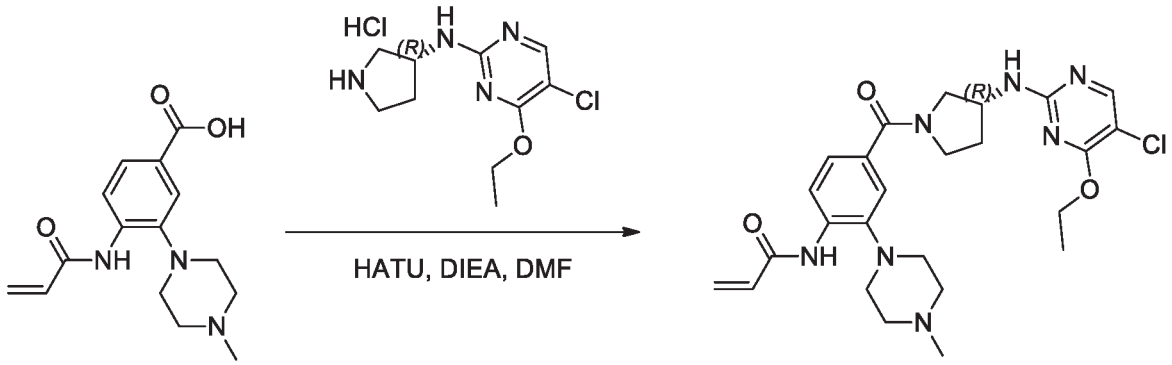
[00532] A mixture of (R)-tert-butyl 3-((4-(dimethylamino)-5-(trifluoromethyl)pyrimidin-2-yl)amino)pyrrolidine-1-carboxylate (350 mg, 0.93 mmol) in HCl/DCM (20 mL) was stirred at RT overnight. The reaction mixture was concentrated to afford (R)-N4,N4-dimethyl-N2-(pyrrolidin-3-yl)-5-(trifluoromethyl)pyrimidine-2,4-diamine (290 mg, 100%) as white solid (HCl salt). [M+H] Calc'd for $C_{11}H_{16}F_3N_5$, 276.1; Found, 276.1

Step 3: (R)-N-(4-(3-((4-(dimethylamino)-5-(trifluoromethyl)pyrimidin-2-yl)amino)pyrrolidine-1-carbonyl)phenyl)acrylamide



[00533] A mixture of (R)-N4,N4-dimethyl-N2-(pyrrolidin-3-yl)-5-(trifluoromethyl)pyrimidine-2,4-diamine (HCl salt) (320 mg, 0.52 mmol), 4-acrylamidobenzoic acid (214 mg, 1.12 mmol), HATU (426 mg, 1.12 mmol) and DIEA (481 mg, 3.73 mmol) in DMF (10 mL) was stirred at RT for overnight. The mixture was diluted with water (50 mL) and extracted with DCM (10 mL* 3). The combined organic layer was washed with brine (20 mL), dried over Na_2SO_4, filtered and concentrated in vacuo. The residue was purified by *prep*-HPLC to afford (R)-N-(4-(3-((4-(dimethylamino)-5-(trifluoromethyl)pyrimidin-2-yl)amino)pyrrolidine-1-carbonyl)phenyl)acrylamide (293.3 mg, 70%) as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ 2.07-2.23 (m, 2H), 3.05 (s, 3H), 3.13 (s, 3H), 3.44-3.65 (m, 3H), 3.82-3.87 (m, 1H), 4.60-4.76 (m, 1H), 5.78 (dd, J = 1.6 Hz, 8.4 Hz, 1H), 6.26-6.30 (m, 1H), 6.42-6.49 (m, 1H), 6.62-6.69 (m, 1H), 7.49-7.53 (m, 2H), 7.71-7.73 (m, 2H), 8.09-8.13 (m, 1H), 10.3 (s, 1H) . [M+H] Calc'd for $C_{21}H_{23}F_3N_6O_2$, 449.2; Found, 449.2

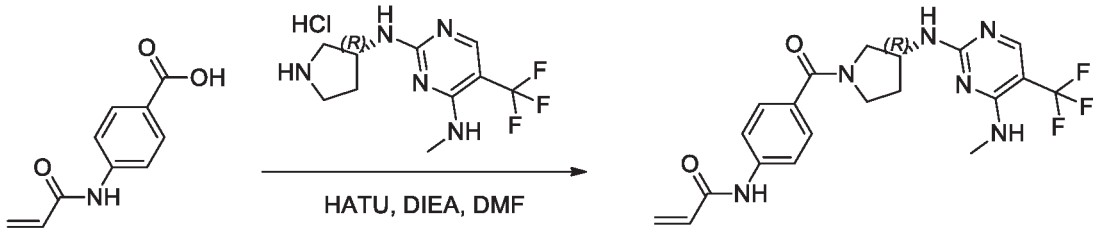
Example 119: Synthesis of (R)-N-(4-(3-((5-chloro-4-ethoxypyrimidin-2-yl)amino)pyrrolidine-1-carbonyl)-2-(4-methylpiperazin-1-yl)phenyl)acrylamide



[00534] A mixture of 4-acrylamido-3-(4-methylpiperazin-1-yl)benzoic acid (150 mg, 0.52 mmol), (R)-5-chloro-4-ethoxy-N-(pyrrolidin-3-yl)pyrimidin-2-amine (HCl salt) (173 mg, 0.62 mmol), HATU (235 mg, 0.62 mmol) and DIEA (201 mg, 1.56 mmol) in DMF (15 mL) was stirred at RT for overnight. The mixture was diluted with water (10 mL) and extracted with DCM (10 mL* 3). The combined organic layer was washed with brine (20 mL), dried over Na_2SO_4, filtered and concentrated in vacuo. The residue was purified by *prep*-HPLC to afford (R)-N-(4-(3-((5-chloro-4-ethoxypyrimidin-2-yl)amino)pyrrolidine-1-carbonyl)-2-(4-methylpiperazin-1-yl)phenyl)acrylamide

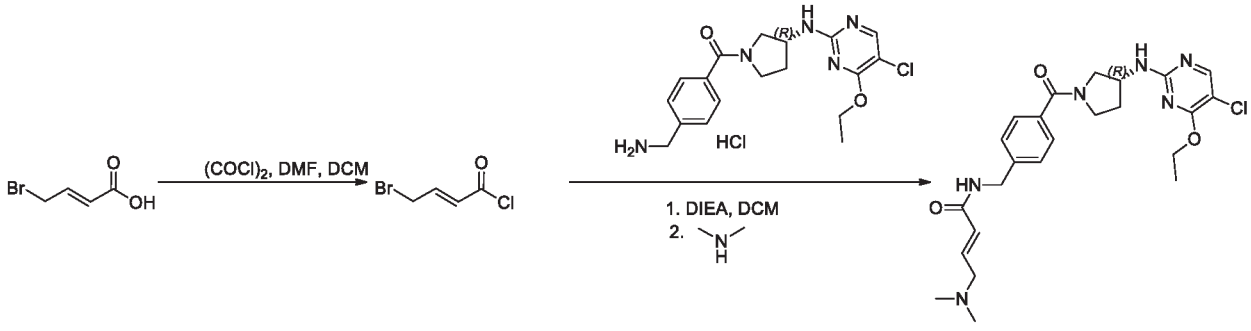
(38.5 mg, 14%) as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.20-1.36 (m, 3H), 1.85-2.03 (m, 1H), 2.06-2.20 (m, 1H), 2.24 (s, 1H), 2.51-2.55 (m, 4H), 2.76-2.86 (m, 4H), 3.40-3.78 (m, 4H), 4.20-4.45 (m, 3H), 5.79 (d, J = 10.0 Hz, 1H), 6.23 (s, 0.5H), 6.28 (s, 0.5H), 6.60-6.67 (m, 1H), 7.22-7.32 (m, 2H), 7.64 (br s, 1H), 8.00-8.13 (m, 2H), 9.08 (s, 0.5H), 9.10 (s, 0.5H). [M+H] Calc'd for $C_{25}H_{32}ClN_7O_3$, 514.2; Found, 514.2

Example 120: Synthesis of (R)-N-(4-(3-((4-(methylamino)-5-(trifluoromethyl)pyrimidin-2-yl)amino)pyrrolidine-1-carbonyl)phenyl)acrylamide

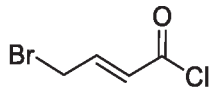


[00535] A mixture of 4-acrylamidobenzoic acid (257 mg, 1.34 mmol), (R)-N4-methyl-N2-(pyrrolidin-3-yl)-5-(trifluoromethyl)pyrimidine-2,4-diamine hydrochloride (363 mg, 1.22 mmol), HATU (510 mg, 1.34 mmol) and DIEA (473 mg, 3.66 mmol) in DMF (20 mL) was stirred at RT for overnight. The mixture was diluted with water (10 mL) and extracted with DCM (10 mL* 3). The combined organic layer was washed with brine (20 mL), dried over Na_2SO_4, filtered and concentrated in vacuo. The residue was purified by *prep*-HPLC to afford (R)-N-(4-(3-((4-(methylamino)-5-(trifluoromethyl)pyrimidin-2-yl)amino)pyrrolidine-1-carbonyl)phenyl)acrylamide (235.6 mg, 46%) as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.91-2.14 (m, 2H), 2.68-2.88 (m, 3H), 3.38-3.42 (m, 1H), 3.53 (s , 1H), 3.63 (d, J = 6.8 Hz, 1H), 3.78-3.87 (m, 1H), 4.31 (s, 0.5H), 4.48 (m, 0.5H), 5.79 (d, J = 10.0 Hz, 1H), 6.26 (s, 0.5H), 6.31 (s, 0.5H), 6.42-6.49 (m, 1H), 6.83-6.92 (m, 1H), 7.49-7.74 (m, 5H), 7.98-8.07 (m, 1H), 10.31 (s, 1H). [M+H] Calc'd for $C_{25}H_{32}ClN_7O_3$, 435.2; Found, 435.2.

Example 121: Synthesis of (R,E)-N-(4-(3-((5-chloro-4-ethoxypyrimidin-2-yl)amino)pyrrolidine-1-carbonyl)benzyl)-4-(dimethylamino)but-2-enamide

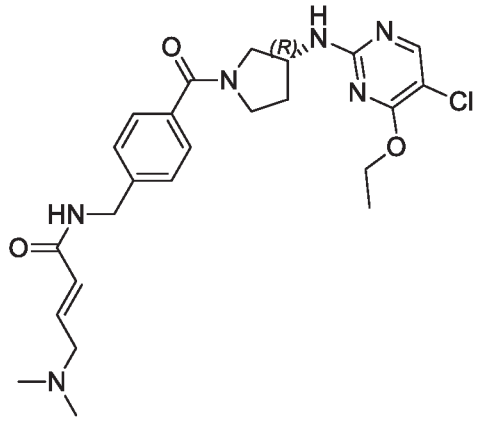


Step 1: (E)-4-bromobut-2-enoyl chloride



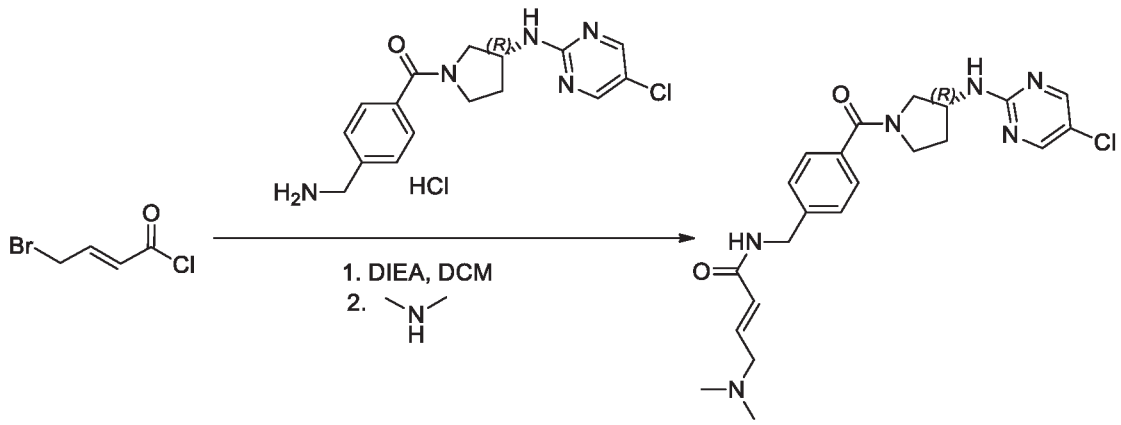
[00536] To a mixture of (E)-4-bromobut-2-enoic acid (400 mg, 2.42 mmol) and DMF (1/4 drops) in DCM (10 mL) was added $(COCl)_2$ (611 mg, 4.85 mmol) at 0°C. The reaction mixture was stirred at RT overnight. The reaction mixture was concentrated in vacuo to afford (E)-4-bromobut-2-enoyl chloride (445 g, 100%) as yellow oil.

Step 2: (R,E)-N-(4-(3-((5-chloro-4-ethoxypyrimidin-2-yl)amino)pyrrolidine-1-carbonyl)benzyl)-4-(dimethylamino)but-2-enamide



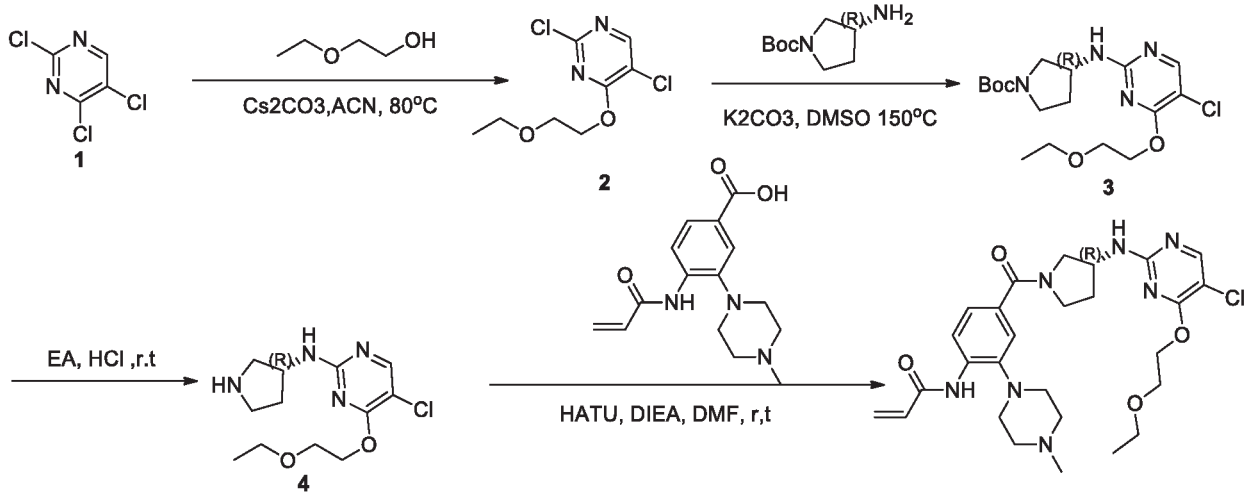
[00537] To a mixture of (R)-(4-(aminomethyl)phenyl)(3-((5-chloro-4-ethoxypyrimidin-2-yl)amino)pyrrolidin-1-yl)methanone HCl salt (400 mg, 0.97 mmol) and DIEA (502 mg, 3.89 mmol) in DCM (15 mL) was added (E)-4-bromobut-2-enoyl chloride (400 mg, 2.42 mmol) at 0 °C. The reaction mixture was stirred at for 2h and dimethylamine (0.98 mL, 1.95 mmol) was added. The reaction mixture was stirred at RT overnight, The mixture was diluted with water (10 mL) and extracted with DCM (10 mL* 3). The combined organic layer was washed with brine (20 mL), dried over Na_2SO_4, filtered and concentrated in vacuo. The residue was purified by *prep*-HPLC to afford (R,E)-N-(4-(3-((5-chloro-4-ethoxypyrimidin-2-yl)amino)pyrrolidine-1-carbonyl)benzyl)-4-(dimethylamino)but-2-enamide (34.5 mg, 7%) as a yellow solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.18-1336 (m, 3H), 1.87-2.00 (m, 2H), 2.14 (s, 6H), 2.97-3.00 (m, 2H), 3.41-3.59 (m, 3H), 3.74-3.79 (m, 1H), 4.23-4.42 (m, 5H), 6.07-6.12 (m, 1H), 6.57-6.64 (m, 1H), 7.27-7.32 (m, 2H), 7.45-7.50 (m, 2H), 7.64 (br s, 1H), 8.07-8.13 (m, 1H), 8.51-8.56 (m, 1H). [M+H] Calc'd for $C_{24}H_{31}ClN_6O_3$, 487.2; Found, 487.2.

Example 122: Synthesis of (R,E)-N-(4-(3-((5-chloropyrimidin-2-yl)amino)pyrrolidine-1-carbonyl)benzyl)-4-(dimethylamino)but-2-enamide

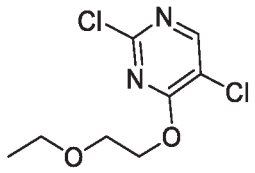


[00538] To a mixture of (R)-(4-(aminomethyl)phenyl)(3-((5-chloropyrimidin-2-yl)amino)pyrrolidin-1-yl)methanone HCl salt (350 mg, 0.820 mmol) and DIEA (529 mg, 4.10 mmol) in DCM (10 mL) was was added (E)-4-bromobut-2-enoyl chloride (180 mg, 0.984 mmol) at 0°C. The reaction mixture was stirred at for 2h and dimethylamine (0.84 mL, 1.64 mmol) was added. The reaction mixture was stirred at RT for overnight, The mixture was diluted with water (10 mL) and extracted with DCM (10 mL* 3). The combined organic layer was washed with brine (20 mL), dried over Na_2SO_4, filtered and concentrated in-vacuo. The residue was purified by *prep*-HPLC to afford (R,E)-N-(4-(3-((5-chloropyrimidin-2-yl)amino)pyrrolidine-1-carbonyl)benzyl)-4-(dimethylamino)but-2-enamide (18.3 mg, 5%) as a yellow solid (TFA salt). ^{1}H NMR (400 MHz, CD_3OD): δ 1.97-2.35 (m, 2H), 2.90 (s, 6H), 3.37-3.41 (m, 1H), 3.52-3.72 (m, 2H), 3.78-3.85 (m, 1H), 3.90-3.94 (m, 2H), 4.36-4.55 (m, 3H), 6.38-6.43 (m, 1H), 6.70-6.79 (m, 1H), 7.36-7.41 (m, 2H), 7.47-7.54 (m, 2H), 8.20 (s, 1H), 8.28 (s, 1H). [M+H] Calc'd for $C_{22}H_{27}ClN_6O_2$, 443.2; Found, 443.2.

Example 123: (R)-N-(4-(3-((5-chloro-4-(2-ethoxyethoxy)pyrimidin-2-yl)amino)pyrrolidine-1-carbonyl)-2-(4-methylpiperazin-1-yl)phenyl)acrylamide

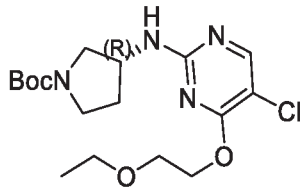


Step 1: 2,5-dichloro-4-(2-ethoxyethoxy)pyrimidine



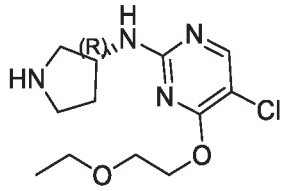
[00539] To a solution of 2,4,5-trichloropyrimidine (2.5 g, 13.7 mmol) and 2-ethoxyethanol (1.1 g, 12.3 mmol) in ACN (40 mL) was added Cs_2CO_3 (6.6 g, 20.5 mmol) at RT. The mixture was stirred at 80°C for 4h. The mixture was cooled, diluted with water (200 mL) and extracted with EA (100 mL*2). The combined organic layer was washed with brine (100 mL), dried over Na_2SO_4 and concentrated. The residue was purified by column chromatography to afford 1.8 g crude product as off white solid. [M+H] Calc'd for $C_8H_{10}Cl_2N_2O_2$, 237.1; Found, 237.1.

Step 2: (R)-tert-butyl 3-((5-chloro-4-(2-ethoxyethoxy)pyrimidin-2-yl)amino)pyrrolidine-1-carboxylate



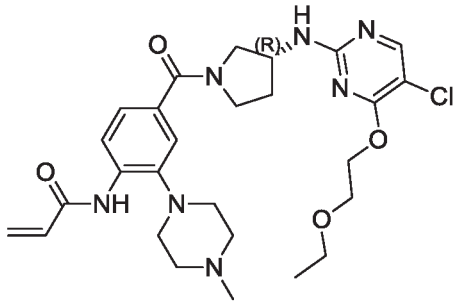
[00540] To a solution of 2,5-dichloro-4-(2-ethoxyethoxy)pyrimidine (1.8 g，7.6 mmol) and (R)-tert-butyl 3-aminopyrrolidine-1-carboxylate (2.8 g, 15.3 mmol)in DMSO (25 mL) was added K_2CO_3 (2.1 g, 15.3 mmol). The reaction mixture was stirred at 150 °C for 4h. The reaction mixture was cooled, added water (50 mL) and extracted with EA (50 mL*2). The combined organic layer was washed with brine (100 mL), dried over Na_2SO_4, filtered and concentrated. The residue was purified by coclumn chromatography to afford 1.8 g of product as colorless oil. [M+H] Calc'd for $C_{17}H_{27}ClN_4O4$, 387.1; Found, 387.1.

Step 3: (R)-5-chloro-4-(2-ethoxyethoxy)-N-(pyrrolidin-3-yl)pyrimidin-2-amine



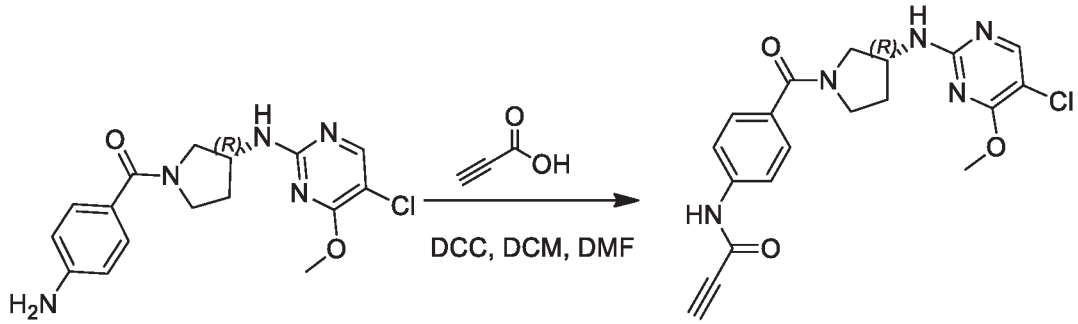
[00541] To a solution of (R)-tert-butyl 3-((5-chloro-4-(2-ethoxyethoxy)pyrimidin-2-yl)amino)pyrrolidine-1-carboxylate (1.8 g, 4.7 mmol) in EA (20 mL) was added HCl(gas) at -50 °C. The reaction mixture was stirred at rt for 3h. The reaction mixture was concentrated to afford 1.5 g of product as a yellow solid. [M+H] Calc'd for $C_{12}H_{19}ClN_4O_2$, 287.1; Found, 287.1.

Step 4：(R)-N-(4-(3-((5-chloro-4-(2-ethoxyethoxy)pyrimidin-2-yl)amino)pyrrolidine-1-carbonyl)-2-(4-methylpiperazin-1-yl)phenyl)acrylamide



[00542] To a solution of (R)-5-chloro-4-(2-ethoxyethoxy)-N-(pyrrolidin-3-yl)pyrimidin-2-amine (200 mg, 0.69 mmol) and 4-acrylamido-3-(4-methylpiperazin-1-yl)benzoic acid (197 mg, 0.69 mmol) in DMF（5 ml）was added HATU (315 mg, 0.83 mmol) and DIEA (267 mg, 2.07 mmol). The reaction mixture was stirred at rt for 2h. The reaction mixture was concentrated. The residue was purified by prep-HPLC to afford (R)-N-(4-(3-((5-chloro-4-(2-ethoxyethoxy)pyrimidin-2-yl)amino)pyrrolidine-1-carbonyl)-2-(4-methylpiperazin-1-yl)phenyl)acrylamide (11.7 mg, 4%) as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6): 1.10-1.11 (m, 3H), 1.90-2,.12 (m, 2H), 2.24 (s, 2H), 2.77-2.83 (m, 4H), 3.41-3.72 (m, 12H), 4.24-4.47 (m, 3H), 5.77-5.79 (d, J = 10.0 Hz, 1H), 6.23 (s, 0.5H), 6.26 (s, 0.5H), 6.60-6.65 (m, 1H), 7.24-7.26 (m, 2H), 7.66 (s, 1H), 8.03-8.15 (m, 2H), 9.05-9.11 (m, 1H); [M+H] Calc'd for $C_{27}H_{36}ClN_7O_4$, 558.2; Found, 558.2.

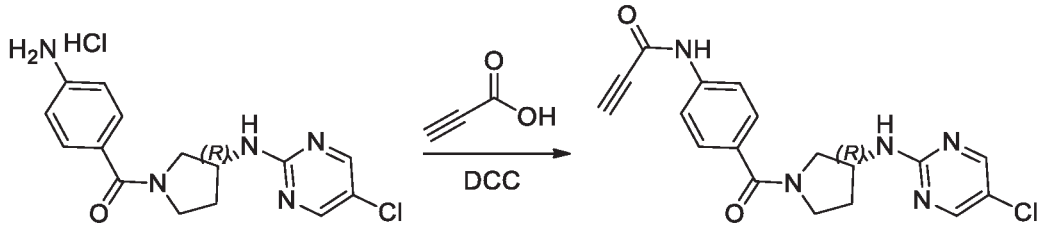
Example 124: Synthesis of (R)-N-(4-(3-((5-chloro-4-methoxypyrimidin-2-yl)amino)pyrrolidine-1-carbonyl)phenyl)propiolamide



[00543] To a solution of propiolic acid (39 mg, 0.56 mmol) in DCM (3 mL) was added DCC (116 mg, 0.56 mmol) slowly at 0°C under N_2. The reaction mixture was stirred at 0 °C for 1 h. Then a solution of (R)-(4-aminophenyl)(3-((5-chloro-4-methoxypyrimidin-2-yl)amino)pyrrolidin-1-yl)methanone (163 mg, 0.47 mmol) in DMF (2 mL) was slowly added. The solution was stirred at 0°C for 90 minutes. Then the reaction mixture was allowed to warm to RT and stirred for overnight. The solution was diluted with EtOAc and washed with water (3 times). The organic phase was concentrated and the residue was purified by *p*rep-HPLC to afford (R)-(4-aminophenyl)(3-((5-chloro-4-methoxypyrimidin-2-yl)amino)pyrrolidin-1-yl)methanone (45.5 mg, 24%) as a light yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$): 1.95-2.06 (m, 1H), 2.19-2.40 (m, 1H), 2.96 (s, 1H),

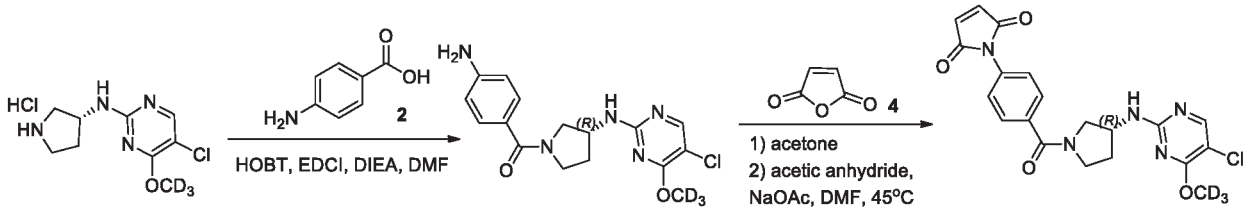
3.35-3.44 (m, 0.5H), 3.54-3.70 (m, 1.5H), 3.74-4.07 (m, 5H), 4.40-4.60 (m, 1H), 5.06-5.30 (m, 1H), 7.46-7.60 (m, 4H), 7.93-8.09 (m, 2H). [M+H] Calc'd for $C_{19}H_{18}ClN_5O_3$, 400.1; Found, 400.1.

Example 125: Synthesis of (*R*)-*N*-(4-(3-((5-chloropyrimidin-2-yl)amino)pyrrolidine-1-carbonyl)phenyl)propiolamide

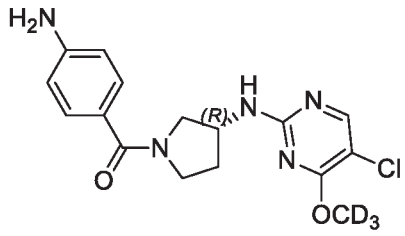


[00544] To a solution of DCC (167 mg, 0.81 mmol) in DCM (2.5 mL) was added propiolic acid (57 mg, 0.81 mmol) at 0°C under N_2. The mixture was stirred at 0°C for 1 hour. Then a solution of (R)-(4-aminophenyl)(3-((5-chloropyrimidin-2-yl)amino)pyrrolidin-1-yl)methanone (235 mg, 0.74 mmol) in DCM (0.5 mL) was added to the reaction mixture. The solution was stirred at 0°C to RT for 16 hours. The solution was diluted with DCM (60 mL), washed with water (20*3 mL) and brine (20 mL), dried over Na_2SO_4 filtered and concentrated. The residue was purified by flash chromatography on silica gel (DCM/MeOH = 50/1) to afford (169 mg, 62%) as a yellow solid. ^1H NMR (400 MHz, $CDCl_3$): δ 1.97-2.01 (m, 1H), 2.23-2.38 (m, 1H), 2.95 (s, 1H), 3.35-3.39 (m, 0.5H), 3.58-3.64 (m, 1H), 3.74-3.88 (m, 2H), 3.99-4.03 (m, 0.5H), 4.42-4.58 (m, 1H), 5.37-5.49 (m, 1H), 7.47-7.57 (m, 4H), 8.18 (s, 1H), 8.25 (s, 1H), 8.48 (s, 0.5H), 8.51 (s, 0.5H). [M+H] Calc'd for $C_{18}H_{16}ClN_5O_2$, 370.0; Found, 370.0

Example 126: Synthesis of (R)-1-(4-(3-((5-chloro-4-(trideuteromethoxy)pyrimidin-2-yl)amino)pyrrolidine-1-carbonyl)phenyl)pyrrolidine-2,5-dione



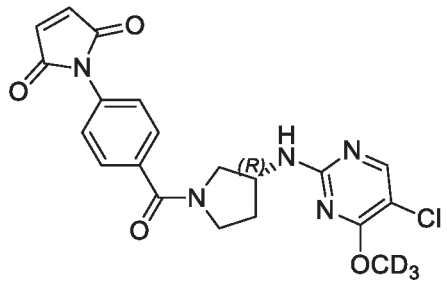
Step 1: (R)-(4-aminophenyl)(3-((5-chloro-4-(trideuteromethoxy)pyrimidin-2-yl)amino)pyrrolidin-1-yl)methanone



[00545] To a solution of (R)-5-chloro-N-(pyrrolidin-3-yl)-4-(trideuteromethoxy)pyrimidin-2-amine hydrochloride (400 mg, 1.49 mmol) and 4-aminobenzoic acid (205 mg, 1.49 mmol) in DMF (6 mL)

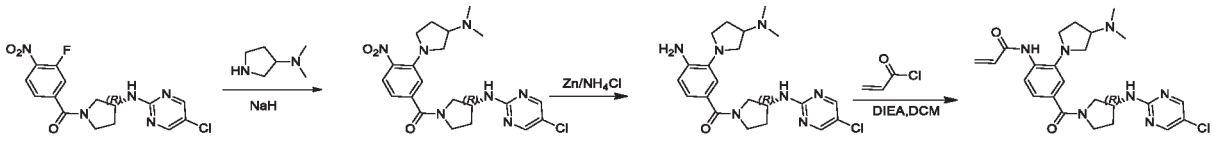
was added HOBT (349 mg, 2.24 mmol), EDCI (429 mg, 2.24 mmol) and DIEA (577 mg, 4.47 mmol) in an ice-bath. The mixture was then stirred at RT for 3 hours. After completion of the reaction, the mixture was diluted with water (20 mL) and the mixture was extracted with EA (20 mL*2). The combined organic layer was ashed with brine, dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure. The residue was purified by C18 reversed phase chromatography (20-95% ACN in H_2O) to afford (R)-(4-aminophenyl)(3-((5-chloro-4-(trideuteromethoxy)pyrimidin-2-yl)amino)pyrrolidin-1-yl)methanone (3) (310 mg, 59% yield) as a white solid. [M +H] Calc'd : $C_{16}H_{15}D_3ClN_5O_2$, 351.1; Found: 351.1.

Step 2: (R)-1-(4-(3-((5-chloro-4-(trideuteromethoxy)pyrimidin-2-yl)amino)pyrrolidine-1-carbonyl)phenyl)pyrrolidine-2,5-dione

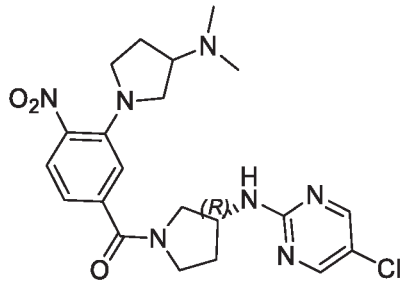


[00546] To a solution of furan-2,5-dione (32 mg, 0.32 mmol) in acetone (2 mL) was added (R)-(4-aminophenyl)(3-((5-chloro-4-(trideuteromethoxy)pyrimidin-2-yl)amino)pyrrolidin-1-yl)methanone (75 mg, 0.21 mmol). The mixture was stirred at 0°C for 20 min. Then the reaction mixture was concentrated under reduced pressure. The residue was dissolved in 2 mL of DMF and heated to 45°C. Acetic anhydride (0.2 mL) and NaOAc (3 mg, 0.04 mmol) were then added with stirring. The mixture was stirred at 45°C for 2 hours. After completion of the reaction, the mixture was diluted with water and the mixture was extracted with DCM (50 mL x 2). The combined organic layer was washed with brine, dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (DCM/MeOH = 80/1) to give the product (R)-1-(4-(3-((5-chloro-4-(trideuteromethoxy)pyrimidin-2-yl)amino)pyrrolidine-1-carbonyl)phenyl)pyrrolidine-2,5-dione (20 mg, 22% yield) as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$): 2.01-2.02 (m, 1H), 2.24-2.39 (m, 1H), 3.40-3.42 (m 0.5H), 3.59-3.90 (m, 3H), 4.02-4.07 (m, 0.5H), 4.46-4.57 (m, 1H), 5.10-5.22 (m, 1H), 6.88 (s, 2H), 7.42-7.47 (m, 2H), 7.61-7.66 (m, 2H), 7.97 (s, 0.5H), 8.04 (s, 0.5H). [M+H] Calc'd for $C_{20}H_{15}D_3ClN_5O_4$, 431.1; Found, 431.2.

Example 127: Synthesis of *N*-(4-((*R*)-3-((5-chloropyrimidin-2-yl)amino)pyrrolidine-1-carbonyl)-2-(3-(dimethylamino)pyrrolidin-1-yl)phenyl)acrylamide

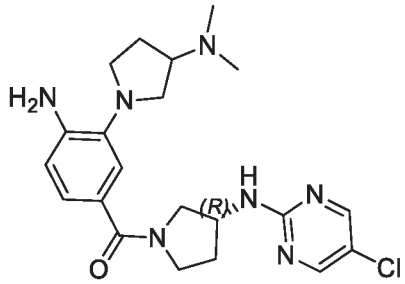


Step 1: ((R)-3-((5-chloropyrimidin-2-yl)amino)pyrrolidin-1-yl)(3-(3-(dimethylamino)pyrrolidin-1-yl)-4-nitrophenyl)methanone



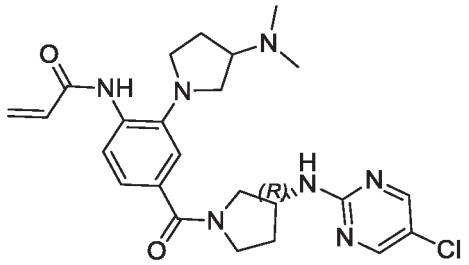
[00547] The title compound was prepared in 32% yield from (*R*)-(3-((5-chloropyrimidin-2-yl)amino)pyrrolidin-1-yl)(3-fluoro-4-nitrophenyl)methanone using general procedure of ((R)-3-((5-chloropyrimidin-2-yl)amino)pyrrolidin-1-yl)(4-nitro-3-((tetrahydrofuran-3-yl)oxy)phenyl)methanone. [M+H] Calc'd for $C_{21}H_{26}ClN_7O_3$, 460.1; Found, 460.1.

Step 2: (4-amino-3-(3-(dimethylamino)pyrrolidin-1-yl)phenyl)((R)-3-((5-chloropyrimidin-2-yl)amino)pyrrolidin-1-yl)methanone



[00548] The title compound was prepared in 100% yield from ((R)-3-((5-chloropyrimidin-2-yl)amino)pyrrolidin-1-yl)(3-(3-(dimethylamino)pyrrolidin-1-yl)-4-nitrophenyl)methanone using general procedure of (4-amino-3-((tetrahydrofuran-3-yl)oxy)phenyl)((R)-3-((5-chloropyrimidin-2-yl)amino)pyrrolidin-1-yl)methanone. [M+H] Calc'd for $C_{21}H_{28}ClN_7O$, 430.2; Found, 430.2.

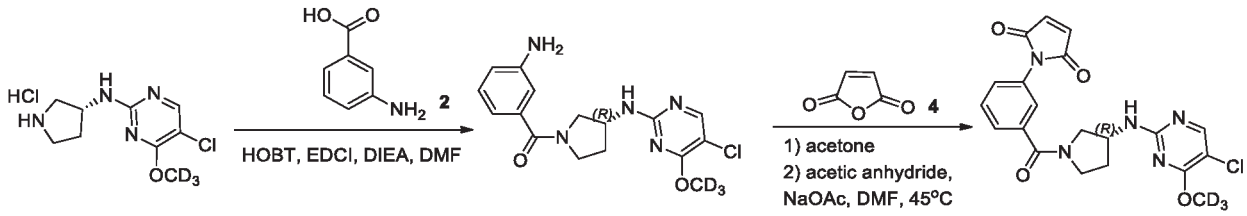
Step 3: N-(4-((R)-3-((5-chloropyrimidin-2-yl)amino)pyrrolidine-1-carbonyl)-2-(3-(dimethylamino)pyrrolidin-1-yl)phenyl)acrylamide



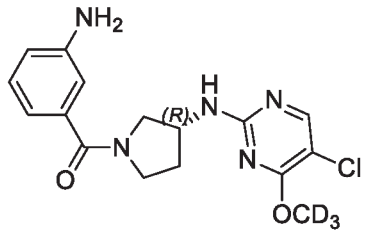
[00549] The title compound was prepared in 30% yield from (4-amino-3-(3-(dimethylamino)pyrrolidin-1-yl)phenyl)((R)-3-((5-chloropyrimidin-2-yl)amino)pyrrolidin-1-yl)methanone using general procedure of (R)-1-(6-(3-((5-chloro-4-methoxypyrimidin-2-yl)amino)pyrrolidine-1-carbonyl)-2-azaspiro[3.3]heptan-2-yl)prop-2-en-1-one. ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.69-1.74 (m, 1H),

1.85-2.00 (m, 1H), 2.02-2.08 (m, 2H), 2.14 (s, 3H), 2.15 (s, 3H), 2.64-2.70 (m, 1H), 3.08-3.77 (m, 8H), 4.23-4.42 (m, 1H), 5.72 (d, J = 10.0 Hz, 1H), 6.22 (d, J = 16.8 Hz, 1H), 6.48-6.54 (m, 1H), 6.87-6.95 (m, 2H), 7.31-7.37 (m, 1H), 7.80-7.83 (m, 1H), 8.32 (s, 1H), 8.38 (s, 1H), 9.48 (br s, 1H). [M+H] Calc'd for $C_{24}H_{30}ClN_7O_2$, 484.2; Found, 484.2.

Example 128: Synthesis of (R)-1-(3-(3-((5-chloro-4-(trideuteriomethoxy)pyrimidin-2-yl)amino)pyrrolidine-1-carbonyl)phenyl)-1H-pyrrole-2,5-dione

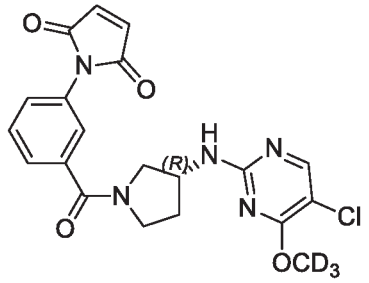


Step 1: (R)-(3-aminophenyl)(3-((5-chloro-4-(trideuteromethoxy)pyrimidin-2-yl)amino)pyrrolidin-1-yl)methanone



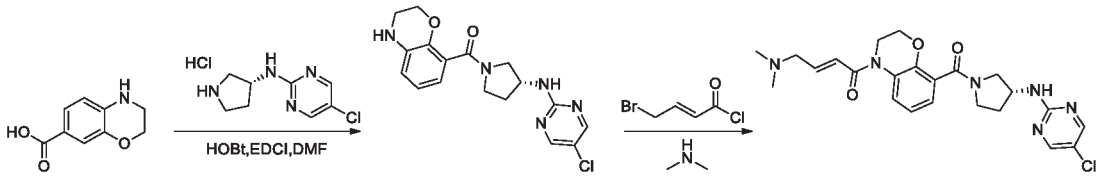
[00550] To a solution of (R)-5-chloro-N-(pyrrolidin-3-yl)-4-(trideuteromethoxy)pyrimidin-2-amine hydrochloride (170 mg, 0.63 mmol) and 3-aminobenzoic acid (87 mg, 0.63 mmol) in DMF (4 mL) was added HOBT (147 mg, 0.95 mmol), EDCI (182 mg, 0.95 mmol) and DIEA (244 mg, 1.89 mmol). The mixture was stirred at rt for 3 hours. After completion of the reaction, the mixture was diluted with water (20 mL) and the mixture was extracted with EA (20 mL*2). The combined organic layer was washed with brine, dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The residue was purified by C18 reversed phase chromatography (20-95% ACN in H_2O) to give the product (R)-(3-aminophenyl)(3-((5-chloro-4-(trideuteriomethoxy)pyrimidin-2-yl)amino)pyrrolidin-1-yl)methanone (105 mg, 48% yield) as a pale yellow solid. [M+H] Calc'd : $C_{16}H_{15}D_3ClN_5O_2$, 351.1; Found: 351.1.

Step 2: (R)-1-(3-(3-((5-chloro-4-(trideuteromethoxy)pyrimidin-2-yl)amino)pyrrolidine-1-carbonyl)phenyl)-1H-pyrrole-2,5-dione

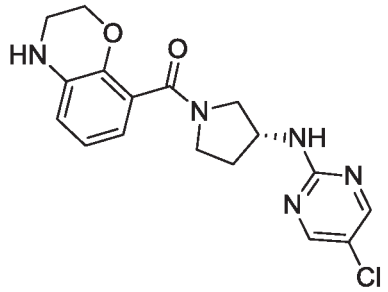


[00551] To a solution of furan-2,5-dione (44 mg, 0.45 mmol) in acetone (2 mL) was added (R)-(3-aminophenyl)(3-((5-chloro-4-(trideuteriomethoxy)pyrimidin-2-yl)amino)pyrrolidin-1-yl)methanone (105 mg, 0.3 mmol). The mixture was stirred at 0°C for 20 min. The reaction mixture was concentrated under reduced pressure. The residue was dissolved in 2 mL of DMF and heated to 45°C. Acetic anhydride (0.2 mL) and NaOAc (5 mg, 0.06 mmol) were then added with stirring. The mixture was stirred at 45°C for 2 hours. After completion of the reaction, the mixture was diluted with water and extracted with DCM (100 mL*2). The combined organic layer was washed with brine, dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (DCM/MeOH = 50/1) to afford (R)-1-(3-(3-((5-chloro-4-(trideuteromethoxy)pyrimidin-2-yl)amino)pyrrolidine-1-carbonyl)phenyl)-1H-pyrrole-2,5-dione (80 mg, 62% yield) as pale yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$): 1.97-2.05 (m, 1H), 2.25-2.38 (m, 1H), 3.46 (dd, *J* = 10.8 Hz, 5.2 Hz, 0.5H), 3.93-3.60 (m, 3H), 4.04 (dd, *J* = 13.2 Hz, 6.4 Hz, 0.5H), 4.45-4.58 (m, 1H), 5.13-5.22 (m, 1H), 6.87 (d, *J* = 4.8 Hz, 2H), 7.45-7.58 (m, 4H),7.97 (s, 0.5H), 8.03 (s, 0.5H). [M+H] Calc'd for $C_{20}H_{15}D_3ClN_5O_4$, 431.1; Found, 431.2.

Example 129: Synthesis of (*R*,*E*)-1-(8-(3-((5-chloropyrimidin-2-yl)amino)pyrrolidine-1-carbonyl)-2*H*-benzo[b][1,4]oxazin-4(3*H*)-yl)-4-(dimethylamino)but-2-en-1-one



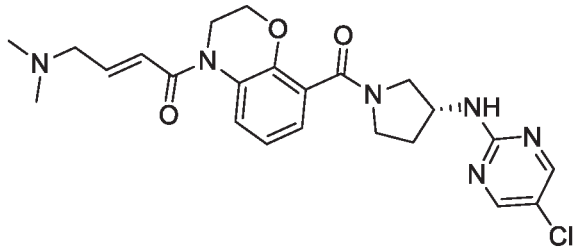
Step 1: (R)-(3-((5-chloropyrimidin-2-yl)amino)pyrrolidin-1-yl)(3,4-dihydro-2H-benzo[b][1,4]oxazin-8-yl)methanone



[00552] A mixture of 3,4-dihydro-2H-benzo[b][1,4]oxazine-7-carboxylic acid (200 mg, 1.1 mmol), (R)-5-chloro-N-(pyrrolidin-3-yl)pyrimidin-2-amine hydrochloride (258 mg, 1.1 mmol), HOBt (223 mg, 1.7 mmol), EDCI (316 mg, 1.7 mmol) and DIEA (426 mg, 3.3 mmol) in DMF (5 mL) was stirred at RT for 5 hours. The mixure was poured into water (30 mL) and extracted with EtOAc (20 mL*3). The combined organic phase was concentrated and the residue was purified by prep- HPLC to afford (*R*)-(3-((5-chloropyrimidin-2-yl)amino)pyrrolidin-1-yl)(3,4-dihydro-2*H*-

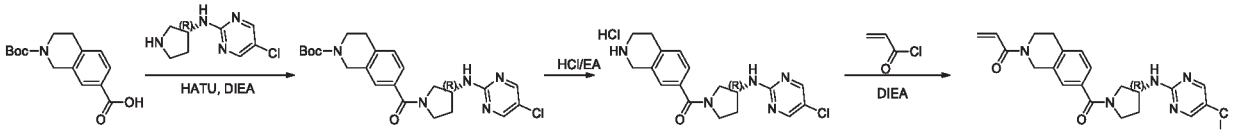
benzo[b][1,4]oxazin-8-yl)methanone (400 mg, 80%) as a red solid. [M+H] Calc'd for $C_{17}H_{18}ClN_5O_2$, 360.1; Found, 360.1..

Step 2: (R,E)-1-(8-(3-((5-chloropyrimidin-2-yl)amino)pyrrolidine-1-carbonyl)-2H-benzo[b][1,4]oxazin-4(3H)-yl)-4-(dimethylamino)but-2-en-1-one

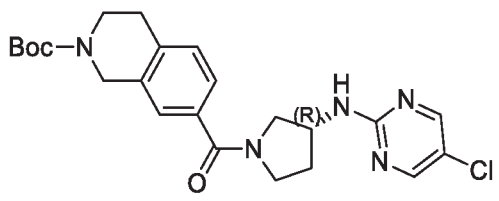


[00553] To a solution of (*R*)-(3-((5-chloropyrimidin-2-yl)amino)pyrrolidin-1-yl)(3,4-dihydro-2*H*-benzo[b][1,4]oxazin-8-yl)methanone (172 mg, 0.48 mmol) and DIEA (310 mg, 2.4 mmol) in DCM (15 mL) was added a solution of (*E*)-4-bromobut-2-enoyl chloride (222 mg, 1.2 mmol) in DCM (5 mL) at 0°C under N_2. The solution was stirred at 0°C for 2 hours. Then dimethylamine (2.4 mL, 4.8 mmol, 2M in THF) was added at 0°C. The solution was stirred at RT for 4 hours. The mixure was poured in to water (30 mL) and extracted with DCM (20 mL*3). The combined organic phase was concentrated and the residue was purified by prep- HPLC to afford (*R,E*)-1-(8-(3-((5-chloropyrimidin-2-yl)amino)pyrrolidine-1-carbonyl)-2*H*-benzo[b][1,4]oxazin-4(3*H*)-yl)-4-(dimethylamino)but-2-en-1-one (44 mg, 19%) as a yellow solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.86-2.03 (m, 1H), 2.13-2.19 (m, 7H), 3.08-3.40 (m, 2H), 3.40-3.47 (m, 1H), 3.51-3.57 (m, 1H), 3.65-3.71 (m, 1H), 3.74-3.82 (m, 1H), 3.95-3.97 (m, 2H), 4.27-4.46 (m, 3H), 6.57-6.63 (m, 1H), 6.77-6.83 (m, 1H), 7.06-7.10 (m, 2H), 7.52 (br s, 1H), 7.86 (d, *J* = 7.2 Hz, 1H), 8.36 (s, 1H), 8.42 (s, 1H). [M+H] Calc'd for $C_{23}H_{27}ClN_6O_3$, 471.1; Found, 471.1.

Example 130: Synthesis of (*R*)-1-(7-(3-((5-chloropyrimidin-2-yl)amino)pyrrolidine-1-carbonyl)-3,4-dihydroisoquinolin-2(1*H*)-yl)prop-2-en-1-one

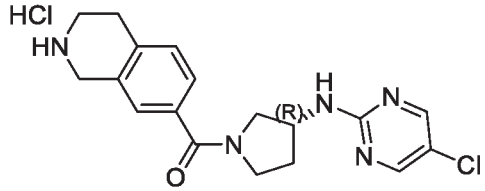


Step 1: (R)-tert-butyl 7-(3-((5-chloropyrimidin-2-yl)amino)pyrrolidine-1-carbonyl)-3,4-dihydroisoquinoline-2(1H)-carboxylate



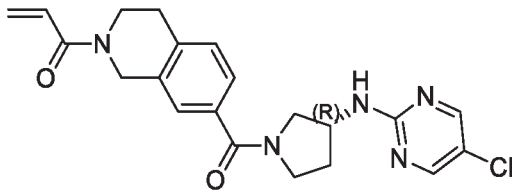
[00554] The title compound was prepared in 91% yield from 2-(tert-butoxycarbonyl)-1,2,3,4-tetrahydroisoquinoline-7-carboxylic acid using general procedure of (*R*)-*N*-(4-(3-((5-chloro-4-methylpyrimidin-2-yl)amino)pyrrolidine-1-carbonyl)phenyl)acrylamide. [M+H] Calc'd for $C_{23}H_{28}ClN_5O_3$, 458.1; Found, 458.1.

Step 2: (R)-(3-((5-chloropyrimidin-2-yl)amino)pyrrolidin-1-yl)(1,2,3,4-tetrahydroisoquinolin-7-yl)methanone hydrochloride



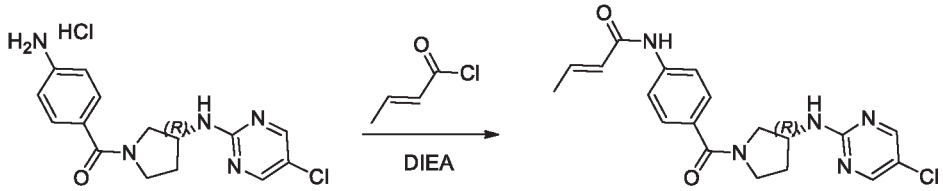
[00555] The title compound was prepared in 100% yield from (R)-tert-butyl 7-(3-((5-chloropyrimidin-2-yl)amino)pyrrolidine-1-carbonyl)-3,4-dihydroisoquinoline-2(1H)-carboxylate using general procedure of (*R*)-5-chloro-4-methyl-*N*-(pyrrolidin-3-yl)pyridin-2-amine hydrochloride [M+H] Calc'd for $C_{18}H_{20}ClN_5O$, 358.1; Found, 358.1.

Step 3: (R)-1-(7-(3-((5-chloropyrimidin-2-yl)amino)pyrrolidine-1-carbonyl)-3,4-dihydroisoquinolin-2(1H)-yl)prop-2-en-1-one



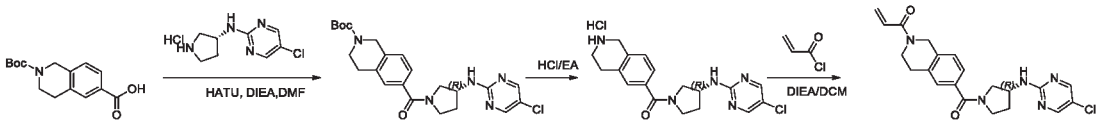
[00556] The title compound was prepared in 37% yield from (R)-(3-((5-chloropyrimidin-2-yl)amino)pyrrolidin-1-yl)(1,2,3,4-tetrahydroisoquinolin-7-yl)methanone hydrochloride using general procedure of (R)-1-(6-(3-((5-chloro-4-methoxypyrimidin-2-yl)amino)pyrrolidine-1-carbonyl)-2-azaspiro[3.3]heptan-2-yl)prop-2-en-1-one. ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.83-2.02 (m, 1H), 2.08-2.20 (m, 1H), 2.76-2.93 (m, 2H), 3.41-3.86 (m, 6H), 4.22-4.44 (m, 1H), 4.61-4.85 (m, 2H), 5.71 (d, J = 10.4 Hz, 1H), 6.10-6.17 (m, 1H), 6.84-6.93 (m, 1H), 7.18-7.25 (m, 1H), 7.29-7.41 (m, 2H), 7.80 (br s, 1H), 8.31 (s, 1H), 8.38 (s, 1H). [M+H] Calc'd for $C_{21}H_{22}ClN_5O_2$, 412.1; Found, 412.1.

Example 131: Synthesis of (*R*,*E*)-*N*-(4-(3-((5-chloropyrimidin-2-yl)amino)pyrrolidine-1-carbonyl)phenyl)but-2-enamide

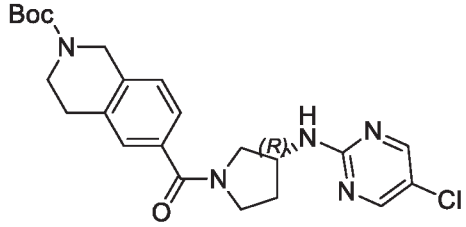


[00557] The title compound was prepared in 28% yield from (R)-(4-aminophenyl)(3-((5-chloropyrimidin-2-yl)amino)pyrrolidin-1-yl)methanone hydrochloride using general procedure of (R)-1-(6-(3-((5-chloro-4-methoxypyrimidin-2-yl)amino)pyrrolidine-1-carbonyl)-2-azaspiro[3.3]heptan-2-yl)prop-2-en-1-one. ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.83-2.00 (m, 1H), 2.07-2.18 (m, 1H), 3.14 (d, J = 6.4 Hz, 2H), 3.40-3.78 (m, 4H), 4.23-4.40 (m, 1H), 5.12-5.20 (m, 2H), 5.90-5.99 (m, 1H), 7.45-7.50 (m, 2H), 7.59-7.64 (m, 2H), 7.80 (br s, 1H), 8.31 (s, 1H), 8.38 (s, 1H), 10.11 (s, 1H). [M+H] Calc'd for $C_{19}H_{20}ClN_5O_2$, 386.1; Found, 386.1.

Example 132: Synthesis of (*R*)-1-(6-(3-((5-chloropyrimidin-2-yl)amino)pyrrolidine-1-carbonyl)-3,4-dihydroisoquinolin-2(1*H*)-yl)prop-2-en-1-one

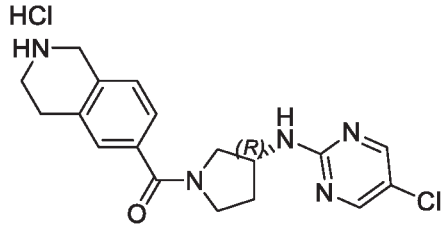


Step 1: (R)-tert-butyl 6-(3-((5-chloropyrimidin-2-yl)amino)pyrrolidine-1-carbonyl)-3,4-dihydroisoquinoline-2(1H)-carboxylate



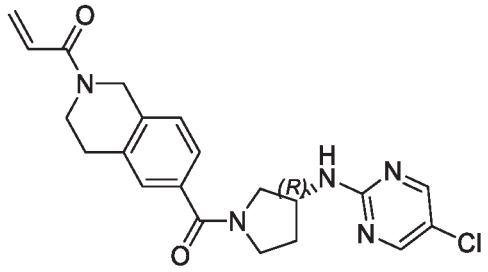
[00558] The title compound was prepared in 75% yield from 2-(tert-butoxycarbonyl)-1,2,3,4-tetrahydroisoquinoline-6-carboxylic acid using general procedure of (*R*)-*N*-(4-(3-((5-chloro-4-methylpyrimidin-2-yl)amino)pyrrolidine-1-carbonyl)phenyl)acrylamide. [M+H] Calc'd for $C_{23}H_{28}ClN_5O_3$, 458.1; Found, 458.1.

Step 2: (R)-(3-((5-chloropyrimidin-2-yl)amino)pyrrolidin-1-yl)(1,2,3,4-tetrahydroisoquinolin-6-yl)methanone hydrochloride



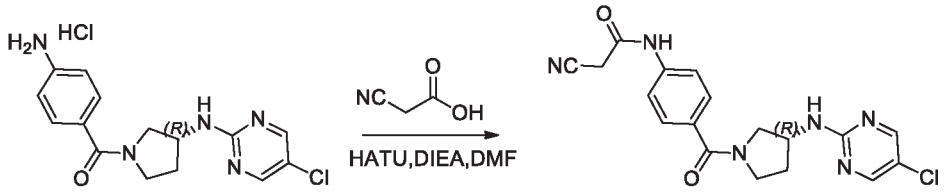
[00559] The title compound was prepared in 100% yield from (R)-tert-butyl 7-(3-((5-chloropyrimidin-2-yl)amino)pyrrolidine-1-carbonyl)-3,4-dihydroisoquinoline-2(1H)-carboxylate using general procedure of (*R*)-5-chloro-4-methyl-*N*-(pyrrolidin-3-yl)pyridin-2-amine hydrochloride [M+H] Calc'd for $C_{18}H_{20}ClN_5O$, 358.1; Found, 358.1.

Step 3: (R)-1-(6-(3-((5-chloropyrimidin-2-yl)amino)pyrrolidine-1-carbonyl)-3,4-dihydroisoquinolin-2(1H)-yl)prop-2-en-1-one



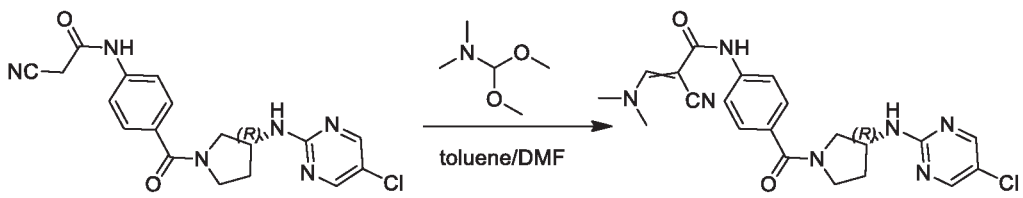
[00560] The title compound was prepared in 41% yield from (R)-(3-((5-chloropyrimidin-2-yl)amino)pyrrolidin-1-yl)(1,2,3,4-tetrahydroisoquinolin-6-yl)methanone hydrochloride using general procedure of (R)-1-(6-(3-((5-chloro-4-methoxypyrimidin-2-yl)amino)pyrrolidine-1-carbonyl)-2-azaspiro[3.3]heptan-2-yl)prop-2-en-1-one. ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.83-2.02 (m, 2H), 2.08-2.20 (m, 2H), 2.81-2.87 (m, 3H), 3.63-3.80 (m, 3H), 4.23-4.42 (m, 1H), 4.68-4.81 (m, 2H), 5.72 (d, J = 10.4 Hz, 1H), 6.15 (d, J = 16.4 Hz, 1H), 6.84-6.92 (m, 1H), 7.21-7.34 (m, 3H), 7.78-7.82 (m, 1H), 8.31 (s, 1H), 8.38 (s, 1H). [M+H] Calc'd for $C_{21}H_{22}ClN_5O_2$, 412.1; Found, 412.1.

Example 133: Synthesis of (*R*)-*N*-(4-(3-((5-chloropyrimidin-2-yl)amino)pyrrolidine-1-carbonyl)phenyl)-2-cyanoacetamide



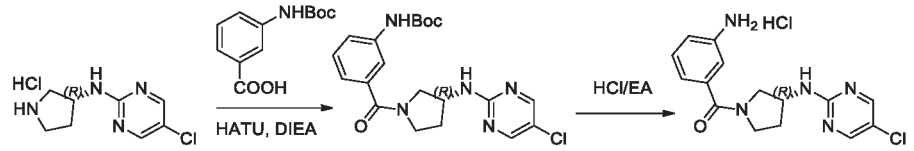
[00561] The title compound was prepared in 34% yield from (*R*)-(4-aminophenyl)(3-((5-chloropyrimidin-2-yl)amino)pyrrolidin-1-yl)methanone hydrochloride using general procedure of (*R*)-*N*-(4-(3-((5-chloro-4-methylpyrimidin-2-yl)amino)pyrrolidine-1-carbonyl)phenyl)acrylamide. ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.88-2.00 (m, 1H), 2.07-2.16 (m, 1H), 3.36-3.74 (m, 4H), 3.92 (s, 2H), 4.23-4.40 (m, 1H), 7.48-7.61 (m, 4H), 7.79-7.82 (m, 1H), 8.31 (s, 1H), 8.38 (s, 1H), 10.45 (s, 1H). [M+H] Calc'd for $C_{18}H_{17}ClN_6O_2$, 385.1; Found, 385.1.

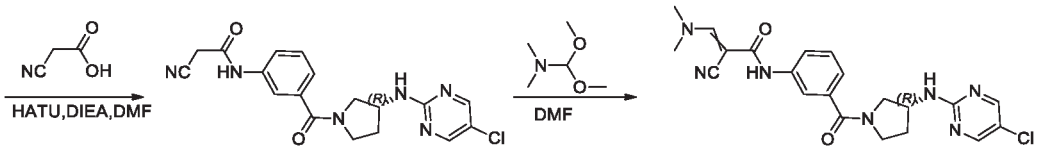
Example 134: Synthesis of (*R*)-*N*-(4-(3-((5-chloropyrimidin-2-yl)amino)pyrrolidine-1-carbonyl)phenyl)-2-cyano-3-(dimethylamino)acrylamide



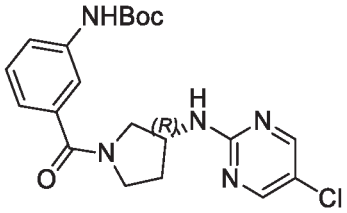
[00562] A mixture of (R)-N-(4-(3-((5-chloropyrimidin-2-yl)amino)pyrrolidine-1-carbonyl)phenyl)-2-cyanoacetamide (100 mg, 0.26 mmol) and 1,1-dimethoxy-N,N-dimethylmethanamine (116 mg, 0.52 mmol) in toluene/DMF (1 mL/ 1 mL) was stirred at 90°C for 2 hours. The mixture was cooled to RT and concentrated. The residue was purified by prep-HPLC to afford (R)-N-(4-(3-((5-chloropyrimidin-2-yl)amino)pyrrolidine-1-carbonyl)phenyl)-2-cyano-3-(dimethylamino)acrylamide (19.8 mg, 17%) as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.88-2.00 (m, 1H), 2.12-2.18 (m, 1H), 3.22 (s, 3H), 3.29 (s, 3H), 3.38-3.44 (m, 1H), 3.52-3.56 (m, 1H), 3.63-3.67 (m, 1H), 3.73-3.80 (m, 1H), 4.23-4.40 (m, 1H), 7.43-7.48 (m, 2H), 7.60-7.65 (m, 2H), 7.80-7.83 (m, 2H), 8.31 (s, 1H), 8.38 (s, 1H), 9.24 (s, 1H). [M+H] Calc'd for $C_{21}H_{22}ClN_7O_2$, 440.1; Found, 440.1.

Example 135: Synthesis of (*R*)-*N*-(3-(3-((5-chloropyrimidin-2-yl)amino)pyrrolidine-1-carbonyl)phenyl)-2-cyano-3-(dimethylamino)acrylamide



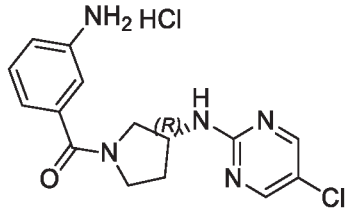


Step 1: (R)-tert-butyl (3-(3-((5-chloropyrimidin-2-yl)amino)pyrrolidine-1-carbonyl)phenyl)carbamate



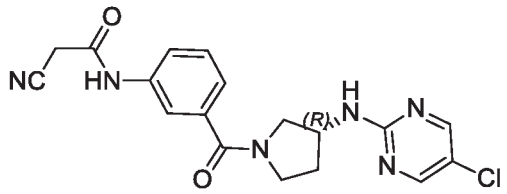
[00563] The title compound was prepared in 45% yield from (*R*)-tert-butyl (3-(3-((5-chloropyrimidin-2-yl)amino)pyrrolidine-1-carbonyl)phenyl)carbamate using general procedure of (*R*)-*N*-(4-(3-((5-chloro-4-methylpyrimidin-2-yl)amino)pyrrolidine-1-carbonyl)phenyl)acrylamide. [M+H] Calc'd for $C_{20}H_{24}ClN_5O_3$, 418.1; Found, 418.1.

Step 2: (R)-(3-aminophenyl)(3-((5-chloropyrimidin-2-yl)amino)pyrrolidin-1-yl)methanone hydrochloride



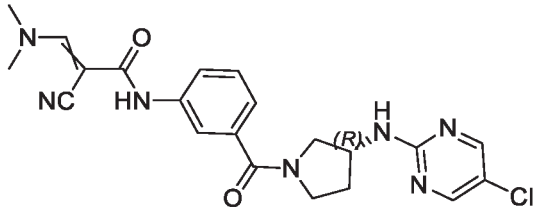
[00564] The title compound was prepared in 100% yield from (*R*)-*tert*-butyl (3-(3-((5-chloropyrimidin-2-yl)amino)pyrrolidine-1-carbonyl)phenyl)carbamate using general procedure of (*R*)-5-chloro-4-methyl-*N*-(pyrrolidin-3-yl)pyridin-2-amine hydrochloride. [M+H] Calc'd for $C_{15}H_{16}ClN_5O$, 318.1; Found, 318.1.

Step 3: (R)-N-(3-(3-((5-chloropyrimidin-2-yl)amino)pyrrolidine-1-carbonyl)phenyl)-2-cyanoacetamide



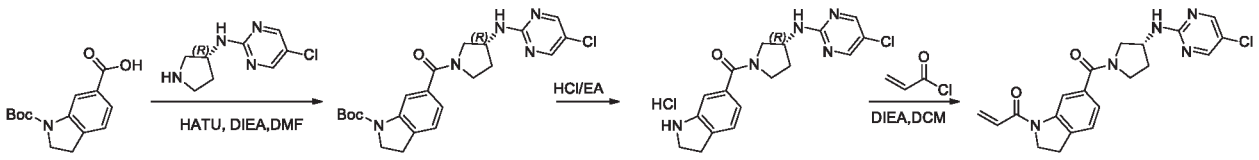
[00565] The title compound was prepared in 37% yield from (*R*)-(3-aminophenyl)(3-((5-chloropyrimidin-2-yl)amino)pyrrolidin-1-yl)methanone hydrochloride using general procedure of (*R*)-*N*-(4-(3-((5-chloro-4-methylpyrimidin-2-yl)amino)pyrrolidine-1-carbonyl)phenyl)acrylamide. [M+H] Calc'd for $C_{18}H_{17}ClN_6O_2$, 385.1; Found, 385.1.

Step 4: (R)-N-(3-(3-((5-chloropyrimidin-2-yl)amino)pyrrolidine-1-carbonyl)phenyl)-2-cyano-3-(dimethylamino)acrylamide

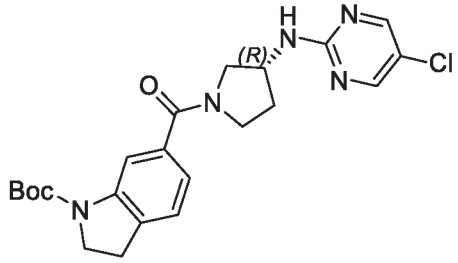


[00566] The title compound was prepared in 36% yield from (*R*)-*N*-(3-(3-((5-chloropyrimidin-2-yl)amino)pyrrolidine-1-carbonyl)phenyl)-2-cyanoacetamide using general procedure of (R)-N-(4-(3-((5-chloropyrimidin-2-yl)amino)pyrrolidine-1-carbonyl)phenyl)-2-cyano-3-(dimethylamino)acrylamide. ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.88-2.00 (m, 1H), 2.11-2.18 (m, 1H), 3.21 (s, 3H), 3.28 (s, 3H), 3.42-3.79 (m, 4H), 4.24-4.39 (m, 1H), 7.11-7.17 (m, 1H), 7.28-7.35 (m, 1H), 7.61-7.64 (m, 1H), 7.74-7.84 (m, 3H), 8.31 (s, 1H), 8.38 (s, 1H), 9.19 (s, 0.5H), 9.22 (s, 0.5H). [M+H] Calc'd for $C_{21}H_{22}ClN_7O_2$, 440.1; Found, 440.1.

Example 136: Synthesis of (*R*)-1-(6-(3-((5-chloropyrimidin-2-yl)amino)pyrrolidine-1-carbonyl)indolin-1-yl)prop-2-en-1-one

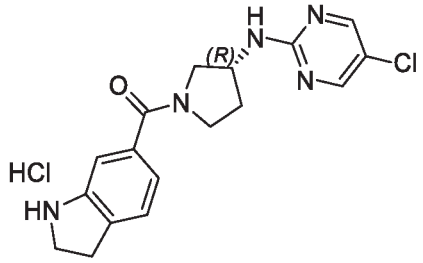


Step 1: (R)-tert-butyl 6-(3-((5-chloropyrimidin-2-yl)amino)pyrrolidine-1-carbonyl)indoline-1-carboxylate



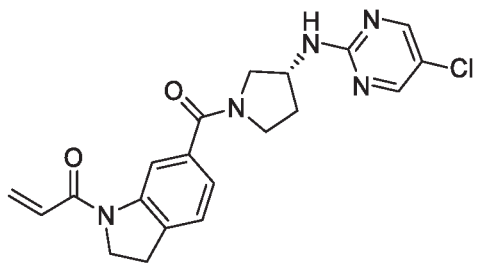
[00567] The title compound was prepared in 67% yield from 1-(tert-butoxycarbonyl)indoline-6-carboxylic acid using general procedure of (*R*)-*N*-(4-(3-((5-chloro-4-methylpyrimidin-2-yl)amino)pyrrolidine-1-carbonyl)phenyl)acrylamide. [M+H] Calc'd for $C_{22}H_{26}ClN_5O_3$, 444.1; Found, 444.1.

Step 2: (R)-(3-((5-chloropyrimidin-2-yl)amino)pyrrolidin-1-yl)(indolin-6-yl)methanone hydrochloride



[00568] The title compound was prepared in 97% yield from (*R*)-*tert*-butyl 6-(3-((5-chloropyrimidin-2-yl)amino)pyrrolidine-1-carbonyl)indoline-1-carboxylat eusing general procedure of (*R*)-5-chloro-4-methyl-*N*-(pyrrolidin-3-yl)pyridin-2-amine hydrochloride [M+H] Calc'd for $C_{17}H_{18}ClN_5O$, 344.1; Found, 344.1.

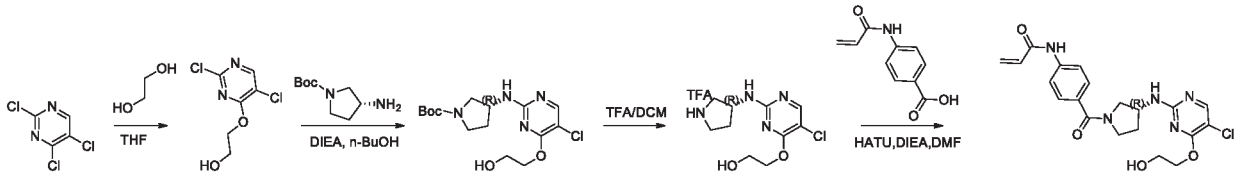
Step 3: (R)-1-(6-(3-((5-chloropyrimidin-2-yl)amino)pyrrolidine-1-carbonyl)indolin-1-yl)prop-2-en-1-one



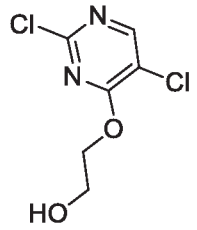
[00569] The title compound was prepared in 15% yield from (*R*)-(3-((5-chloropyrimidin-2-yl)amino)pyrrolidin-1-yl)(indolin-6-yl)methanone hydrochloride using general procedure of (R)-1-

(6-(3-((5-chloro-4-methoxypyrimidin-2-yl)amino)pyrrolidine-1-carbonyl)-2-azaspiro[3.3]heptan-2-yl)prop-2-en-1-one. ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.85-2.02 (m, 1H), 2.07-2.12 (m, 1H), 3.12-3.15 (m, 2H), 3.44-3.79 (m, 4H), 4.21-4.40 (m, 3H), 5.80-5.83 (m, 1H), 6.30 (d, J = 16.4 Hz, 1H), 6.70-6.77 (m, 1H), 7.11-7.15 (m, 1H), 7.28-7.31 (m, 1H), 7.80-7.87 (m, 1H), 8.28-8.31 (m, 2H), 8.40 (s, 1H). [M+H] Calc'd for $C_{20}H_{20}ClN_5O_2$, 398.1; Found, 398.1.

Example 137: Synthesis of (*R*)-*N*-(4-(3-((5-chloro-4-(2-hydroxyethoxy)pyrimidin-2-yl)amino)pyrrolidine-1-carbonyl)phenyl)acrylamide

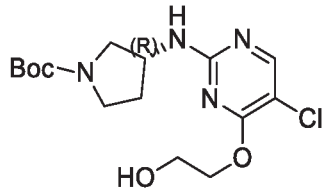


Step 1: 2-((2,5-dichloropyrimidin-4-yl)oxy)ethanol



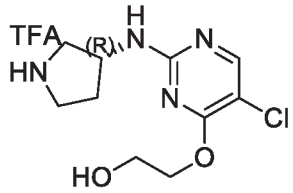
[00570] To a solution of 2,4,5-trichloropyrimidine (500 mg, 2.7 mmol) in THF (5 mL) was added ethane-1,2-diol (226 mg, 2.7 mmol) dropwise at 0 °C. The mixture was stirred at 0 °C for 30 minutes. The mixture was purified by flash chromatography on silica gel (petroleum ether/EtOAc = 10/1) to afford 2-((2,5-dichloropyrimidin-4-yl)oxy)ethanol (360 mg, 64%) as a white solid. [M+H] Calc'd for $C_6H_6Cl_2N_2O_2$, 208.9; Found, 208.9.

Step 2: (R)-tert-butyl 3-((5-chloro-4-(2-hydroxyethoxy)pyrimidin-2-yl)amino)pyrrolidine-1-carboxylate



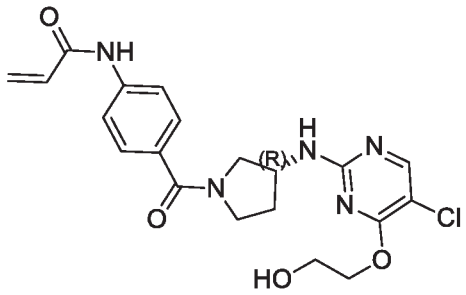
[00571] The title compound was prepared in 93% yield from 2-((2,5-dichloropyrimidin-4-yl)oxy)ethanol using general procedure of (*R*)-*tert*-butyl 3-((5-chloro-4-methylpyrimidin-2-yl)amino)pyrrolidine-1-carboxylate. [M+H] Calc'd for $C_{15}H_{23}ClN_4O_4$, 359.1; Found, 359.1.

Step 3: (R)-2-((5-chloro-2-(pyrrolidin-3-ylamino)pyrimidin-4-yl)oxy)ethanol 2,2,2-trifluoroacetate



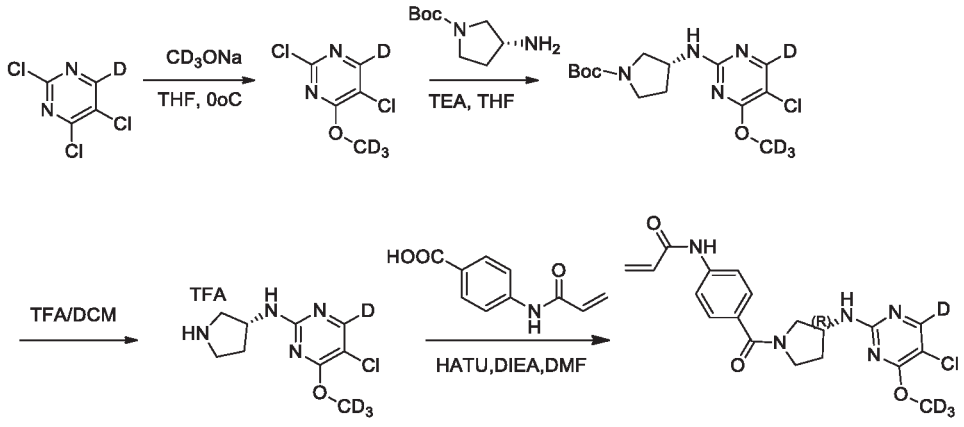
[00572] The title compound was prepared in 100% yield from (*R*)-*tert*-butyl 3-((5-chloro-4-(2-hydroxyethoxy)pyrimidin-2-yl)amino)pyrrolidine-1-carboxylate using general procedure of (*R*)-5-chloro-4-methyl-N-(pyrrolidin-3-yl)pyrimidin-2-amine 2,2,2-trifluoroacetate. [M+H] Calc'd for $C_{10}H_{15}ClN_4O_2$, 259.0; Found, 259.0.

Step 4: (R)-N-(4-(3-((5-chloro-4-(2-hydroxyethoxy)pyrimidin-2-yl)amino)pyrrolidine-1-carbonyl)phenyl)acrylamide

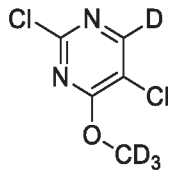


[00573] The title compound was prepared in 13% yield from (R)-2-((5-chloro-2-(pyrrolidin-3-ylamino)pyrimidin-4-yl)oxy)ethanol 2,2,2-trifluoroacetate using general procedure of (*R*)-*N*-(4-(3-((5-chloro-4-methylpyrimidin-2-yl)amino)pyrrolidine-1-carbonyl)phenyl)acrylamide. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.88-2.00 (m, 1H), 2.07-2.14 (m, 1H), 3.37-3.78 (m, 6H), 4.24-4.38 (m, 3H), 4.84-4.90 (m, 1H), 5.78 (d, *J* = 10.0 Hz, 1H), 6.28 (d, *J* = 16.8 Hz, 1H), 6.41-6.48 (m, 1H), 7.49-7.54 (m, 2H), 7.61-7.67 (m, 3H), 8.07 (s, 0.5H), 8.14 (s, 0.5H), 10.32 (s, 1H). [M+H] Calc'd for $C_{20}H_{22}ClN_5O_4$, 432.1; Found, 432.1.

<u>Example 138: Synthesis of (R)-N-(4-(3-((5-chloro-4-deutero-6-(trideuteromethoxy)pyrimidin-2-yl)amino)pyrrolidine-1-carbonyl)phenyl)acrylamide</u>

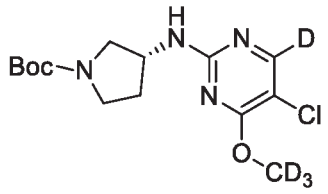


Step 1: 2,5-dichloro-4-deutero-6-(trideuteromethoxy)pyrimidine



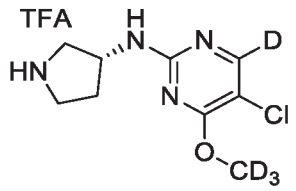
[00574] To a solution of 2,4,5-trichloro-6-deuteropyrimidine (200 mg, 1.08 mmol) in THF (2 mL) was added CD_3ONa (62 mg, 1.08 mmol) at 0°C. The mixture was stirred at 0°C for 30 minutes. The mixture was concentrated. The residue was purified by flash chromatography on silica gel (PE) to afford 2,5-dichloro-4-deutero-6-(trideuteromethoxy)pyrimidine (180 mg, 91%) as yellow oil. [M+H] Calc'd for $C_5D_4Cl_2N_2O$, 183.9; Found, 183.9.

Step 2: (R)-tert-butyl 3-((5-chloro-4-deutero-6-(trideuteromethoxy)pyrimidin-2-yl)amino)pyrrolidine-1-carboxylate



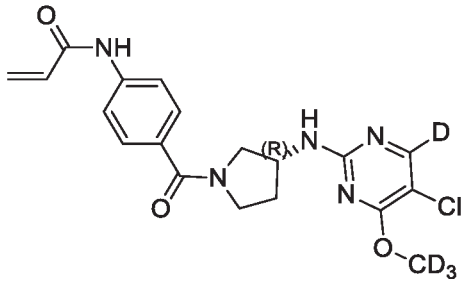
[00575] 2,5-dichloro-4-deutero-6-(trideuteromethoxy)pyrimidine (180 mg, 1.01 mmol), (*R*)-*tert*-butyl 3-aminopyrrolidine-1-carboxylate (186 mg, 1.01 mmol) and TEA (303 mg, 3.0 mmol) in THF (4 mL) were combined at RT. The mixture was then stirred at 75°C for 30 minutes. The mixture was concentrated and the resultant residue was purified by flash chromatography on silica gel (PE/EA = 10/1) to afford(R)-tert-butyl 3-((5-chloro-4-deutero-6-(trideuteromethoxy)pyrimidin-2-yl)amino)pyrrolidine-1-carboxylate (150 mg, 46%) as a white solid. [M+H] Calc'd for $C_{14}H_{17}D_4ClN_4O_3$, 333.1; Found, 333.1.

Step 3: (R)-5-chloro-4-deutero-N-(pyrrolidin-3-yl)-6-(deuteromethoxy)pyrimidin-2-amine 2,2,2-trifluoroacetate



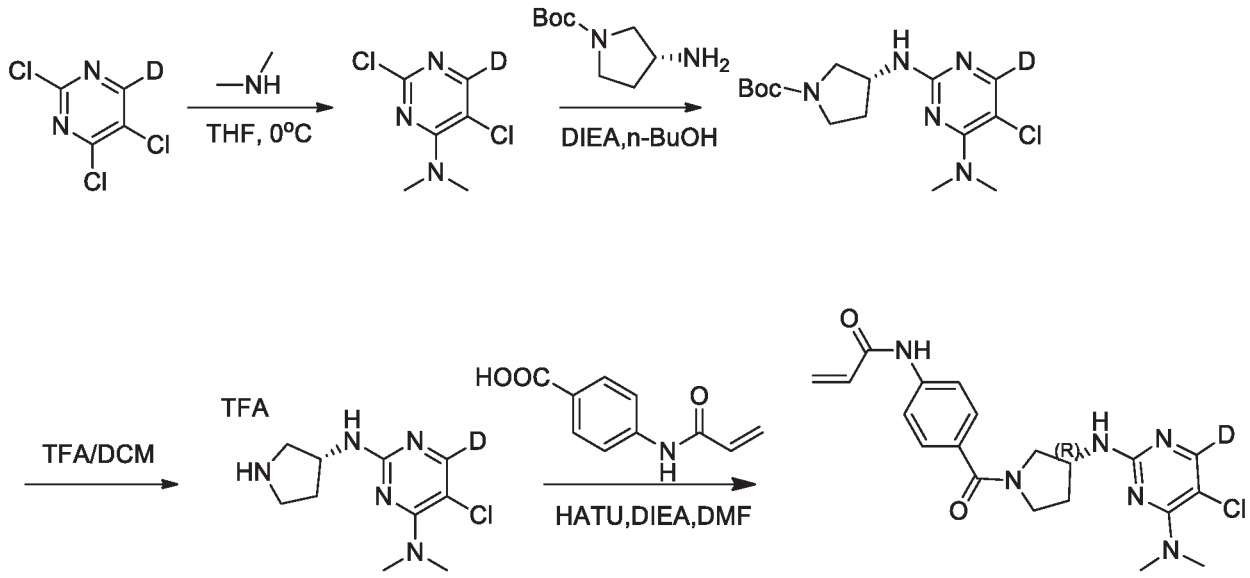
[00576] The title compound was prepared in 100% yield from(R)-tert-butyl 3-((5-chloro-4-deutero-6-(trideuteromethoxy)pyrimidin-2-yl)amino)pyrrolidine-1-carboxylate using general procedure of (*R*)-5-chloro-4-methyl-N-(pyrrolidin-3-yl)pyrimidin-2-amine 2,2,2-trifluoroacetate. [M+H] Calc'd for $C_9H_9D_4ClN_4O$, 233.1; Found, 233.1.

Step 4: (R)-N-(4-(3-((5-chloro-4-deutero-6-(trideuteromethoxy)pyrimidin-2-yl)amino)pyrrolidine-1-carbonyl)phenyl)acrylamide

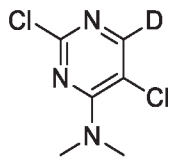


[00577] The title compound was prepared in 11% yield from (R)-5-chloro-4-deutero-N-(pyrrolidin-3-yl)-6-(deuteromethoxy)pyrimidin-2-amine 2,2,2-trifluoroacetate using general procedure of (*R*)-*N*-(4-(3-((5-chloro-4-methylpyrimidin-2-yl)amino)pyrrolidine-1-carbonyl)phenyl)acrylamide. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.97-2.03 (m, 1H), 2.21-2.37 (m, 1H), 3.39-4.04 (m, 4H), 4.44-4.56 (m, 1H), 5.17-5.41 (m, 1H), 5.79 (d, *J* = 10.0 Hz, 1H), 6.24-6.31 (m, 1H), 6.46 (d, *J* = 16.8 Hz, 1H), 7.47-7.52 (m, 2H), 7.58-7.65 (m, 2H), 7.67-7.72 (m, 1H). [M+H] Calc'd for $C_{19}H_{16}D_4ClN_5O_3$, 406.1; Found, 406.1.

Example 139: Synthesis of (R)-N-(4-(3-((5-chloro-4-(dimethylamino)-6-deuteropyrimidin-2-yl)amino)pyrrolidine-1-carbonyl)phenyl)acrylamide

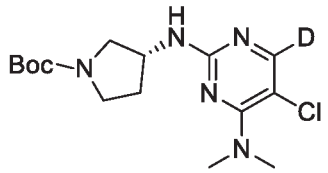


Step 1: 2,5-dichloro-6-deutero-N,N-dimethylpyrimidin-4-amine



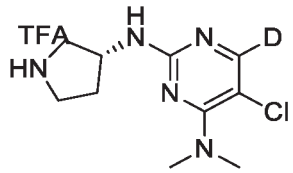
[00578] The title compound was prepared in 67% yield from4,5-trichloro-6-deuteropyrimidineusing general procedure of 2,5-dichloro-*N*,*N*-dimethylpyrimidin-4-amine. [M+H] Calc'd for $C_6H_6DCl_2N_3$, 193.0; Found, 193.0

Step 2: (R)-tert-butyl 3-((5-chloro-4-(dimethylamino)-6-deuteropyrimidin-2-yl)amino)pyrrolidine-1-carboxylate



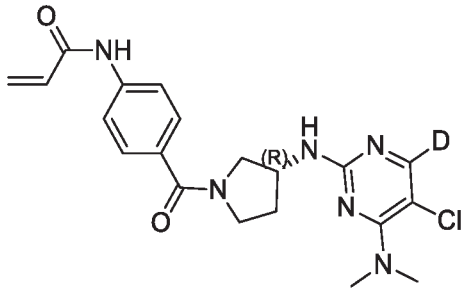
[00579] The title compound was prepared in 31% yield from 2,5-dichloro-6-deutero-N,N-dimethylpyrimidin-4-amine using general procedure of (*R*)-*tert*-butyl 3-((5-chloro-4-methylpyrimidin-2-yl)amino)pyrrolidine-1-carboxylate. [M+H] Calc'd for $C_{15}H_{23}DClN_5O_2$, 343.1; Found, 343.1.

Step 3: (R)-5-chloro-6-deutero-N4,N4-dimethyl-N2-(pyrrolidin-3-yl)pyrimidine-2,4-diamine



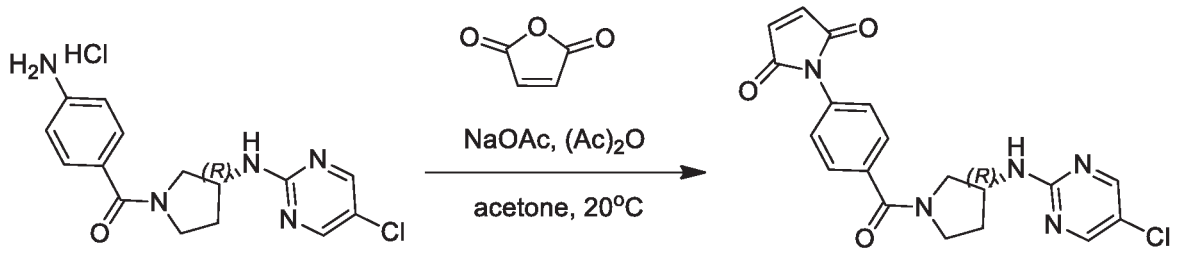
[00580] The title compound was prepared in 100% yield from(R)-tert-butyl 3-((5-chloro-4-(dimethylamino)-6-deuteropyrimidin-2-yl)amino)pyrrolidine-1-carboxylate using general procedure of (*R*)-5-chloro-4-methyl-N-(pyrrolidin-3-yl)pyrimidin-2-amine 2,2,2-trifluoroacetate. [M+H] Calc'd for $C_{10}H_{15}DClN_5$, 243.1; Found, 243.1.

Step 4: (R)-N-(4-(3-((5-chloro-4-(dimethylamino)-6-deuteropyrimidin-2-yl)amino)pyrrolidine-1-carbonyl)phenyl)acrylamide



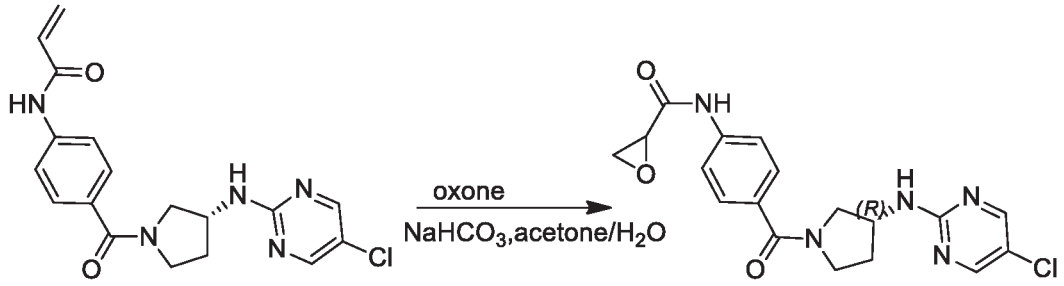
[00581] The title compound was prepared in 43% yield from(R)-5-chloro-6-deutero-N4,N4-dimethyl-N2-(pyrrolidin-3-yl)pyrimidine-2,4-diamine using general procedure of (*R*)-*N*-(4-(3-((5-chloro-4-methylpyrimidin-2-yl)amino)pyrrolidine-1-carbonyl)phenyl)acrylamide. ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.87-1.98 (m, 1H), 2.12-2.19 (m, 1H), 3.02 (s, 3H), 3.10 (s, 3H), 3.42-3.77 (m, 4H), 4.19-4.36 (m, 1H), 5.78 (d, J = 10.0 Hz, 1H), 6.28 (d, J = 16.8 Hz, 1H), 6.41-6.48 (m, 1H), 7.16 (br s, 1H), 7.48-7.53 (m, 2H), 7.69-7.73 (m, 2H), 10.30 (s, 1H). [M+H] Calc'd for $C_{20}H_{22}DClN_6O_2$, 416.1; Found, 416.1.

Example 140: Synthesis of (R)-1-(4-(3-((5-chloropyrimidin-2-yl)amino)pyrrolidine-1-carbonyl) phenyl)-1H-pyrrole-2,5-dione



A mixture of (R)-(4-aminophenyl)(3-((5-chloropyrimidin-2-yl)amino)Pyrrolidin-1-yl)methanone (310 mg, 0.87 mmol) and furan-2,5-dione (121.8 mg, 1.74 mmol) in acetone (5 mL) was stirred at 20°C for 2 hrs. The reaction mixture was concentrated under reduced pressure. To this residue was added a solution of sodium acetate (76.3 mg, 0.87 mmol) and acetic anhydride (177 mg, 1.74 mmol) in DMF (3 mL). The mixture was stirred at 50°C for 5 hrs. The reaction was filtered and concentrated and the residue was purified by silica gel chromatography (DCM/MeOH= 20/1) to afford (R)-1-(4-(3-((5-chloropyrimidin-2-yl)amino)pyrrolidine-1-carbonyl)phenyl)-1H-pyrrole-2,5-dione (142.6 mg, 41%) as a yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$): 1.99-2.03 (m, 1H), 2.26-2.40 (m, 1H), 3.36-4.07 (m, 4H), 4.44-4.58 (m, 1H), 5.23-5.33 (m, 1H), 6.72-6.87 (m, 2H), 7.38-7.46 (m, 2H), 7.54-7.65 (m, 2H), 8.19-8.25 (m, 2H); [M+H] Calc'd for $C_{19}H_{16}ClN_5O_3$, 398.1; Found, 398.1.

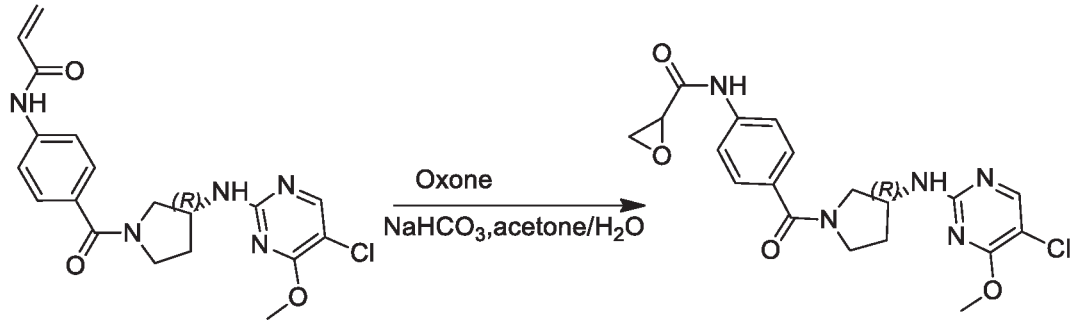
Example 141: Synthesis of *N*-(4-((*R*)-3-((5-chloropyrimidin-2-yl)amino)pyrrolidine-1-carbonyl)phenyl)oxirane-2-carboxamide



[00582] To a mixture of (*R*)-*N*-(4-(3-((5-chloropyrimidin-2-yl)amino)pyrrolidine-1-carbonyl)phenyl)acrylamide (300 mg, 0.81 mmol) in acetone/H_2O (6 mL/ 6 mL) was added $NaHCO_3$ (299 mg, 3.56 mmol) and oxone (996 mg, 1.62 mmol) portionwise at 0°C. The mixture was stirred at RT for 3 hours. The mixture was poured to sat. $NaHCO_3$ (15 mL) and extracted with EtOAc (20 mL*2). The combined organic phase was washed with brine (20 mL), dried over Na_2SO_4, filtered and concentrated. The residue was purified by prep-HPLC to afford *N*-(4-((*R*)-3-((5-chloropyrimidin-2-yl)amino)pyrrolidine-1-carbonyl)phenyl)oxirane-2-carboxamide (23.9 mg, 8%) as a yellow solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ 2.07-2.17 (m, 2H), 3.51-3.56 (m, 2H),

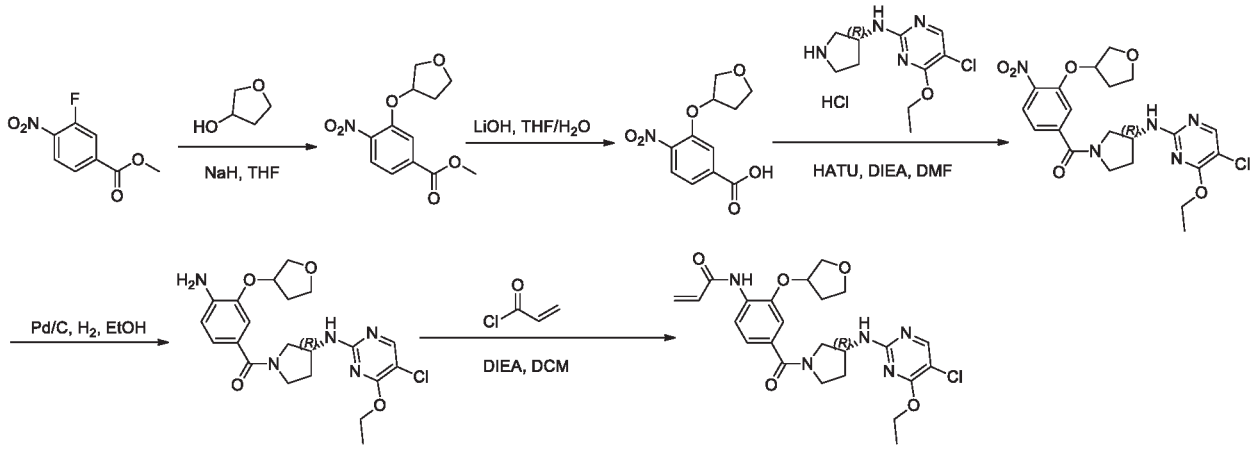
3.62-3.68 (m, 1H), 3.76-3.83 (m, 1H), 4.40-4.53 (m, 1H), 5.76-5.80 (m, 1H), 6.27 (d, J = 16.0 Hz, 1H), 6.41-6.47 (m, 1H), 7.49-7.53 (m, 2H), 7.69-7.73 (m, 2H), 7.97 (s, 0.5H), 8.06 (s, 0.5H), 8.26-8.33 (m, 1H), 8.77 (s, 0.5H), 8.81 (s, 0.5H), 10.29 (s, 1H); [M+H] Calc'd for $C_{18}H_{18}ClN_5O_3$: 388.1; Found: 388.1.

Example 142: Synthesis of *N*-(4-((*R*)-3-((5-chloro-4-methoxypyrimidin-2-yl)amino)pyrrolidine-1-carbonyl)phenyl)oxirane-2-carboxamide

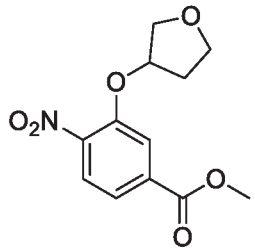


[00583] The title compound was prepared in 11% yield from (*R*)-*N*-(4-(3-((5-chloro-4-methoxypyrimidin-2-yl)amino)pyrrolidine-1-carbonyl)phenyl)acrylamide using general procedure of *N*-(4-((*R*)-3-((5-chloropyrimidin-2-yl)amino)pyrrolidine-1-carbonyl)phenyl)oxirane-2-carboxamide. ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.08-2.15 (m, 1H), 2.28-2.42 (m, 1H), 3.48-3.84 (m, 3H), 4.93-4.06 (m, 4H), 4.48-4.57 (m, 1H), 5.79 (s, 0.5H), 5.82 (s, 0.5H), 6.24-6.31 (m, 1H), 6.44 (s, 0.6H), 6.48 (s, 0.4H), 7.34-7.38 (m, 1H), 7.50-7.54 (m, 2H), 7.58-7.62 (m, 2H), 7.72 (s, 1H), 8.21-8.24 (m, 1H). [M+H] Calc'd for $C_{19}H_{20}ClN_5O_4$, 418.1; Found, 418.1.

Example 143: Synthesis of N-(4-((R)-3-((5-chloro-4-ethoxypyrimidin-2-yl)amino)pyrrolidine-1-carbonyl)-2-((tetrahydrofuran-3-yl)oxy)phenyl)acrylamide

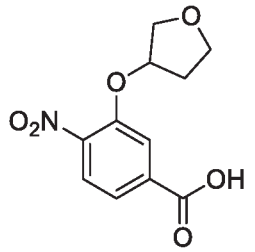


Step 1: methyl 4-nitro-3-((tetrahydrofuran-3-yl)oxy)benzoate



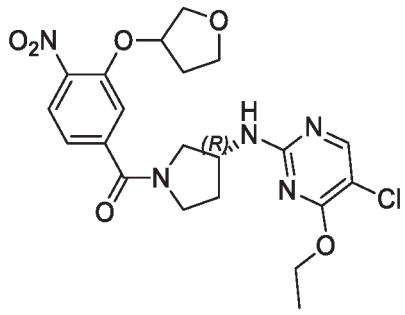
[00584] To a mixture of tetrahydrofuran-3-ol (884 mg, 10.0mmol) in THF (10 mL) was added NaH (884 mg, 11.0 mmol) at 0°C. After the reaction mixture was stirred at for 20 min, methyl 3-fluoro-4-nitrobenzoate (2.0 g, 10.1 mmol) was added. The reaction mixture was then stirred at RT overnight, The mixture was diluted with water (10 mL) and extracted with DCM (10 mL* 3). The combined organic layer was washed with brine (20 mL), dried over Na_2SO_4, filtered and concentrated and purified by silica gel chromatography (PE/EA = 1 ~ 10/1) to afford methyl 4-nitro-3-((tetrahydrofuran-3-yl)oxy)benzoate (717 mg, 27%) as yellow solid. [M+H] Calc'd for $C_{12}H_{13}NO_6$, 268.1; Found, 268.1

Step 2: 4-nitro-3-((tetrahydrofuran-3-yl)oxy)benzoate



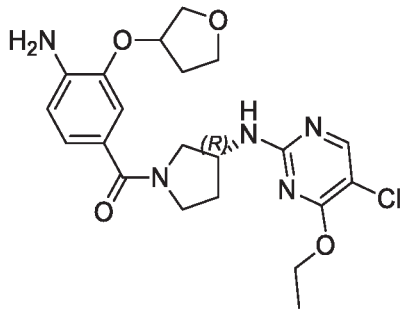
[00585] A mixture of methyl 4-nitro-3-((tetrahydrofuran-3-yl)oxy)benzoate (350 mg, 1.31 mmol) and LiOH (83 mg, 1.97 mmol) in THF/H_2O (10 mL /5 mL) was stirred at RT for overnight, The mixture was adjusted to pH 5 and extracted with DCM (10 mL*3). The combined organic layer was washed with brine (20 mL), dried over Na_2SO_4, filtered and concentrated to afford 4-nitro-3-((tetrahydrofuran-3-yl)oxy)benzoic acid (330 mg, 100%) as a yellow solid. [M+H] Calc'd for $C_{11}H_{11}NO_6$, 254.0; Found, 254.0

Step 3: ((R)-3-((5-chloro-4-ethoxypyrimidin-2-yl)amino)pyrrolidin-1-yl)(4-nitro-3-((tetrahydrofuran-3-yl)oxy)phenyl)methanone



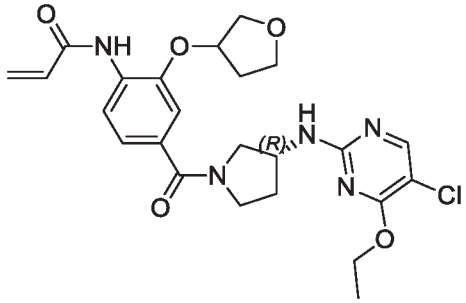
[00586] A mixture of 4-nitro-3-((tetrahydrofuran-3-yl)oxy)benzoic acid (330 mg, 1.31 mmol), (R)-5-chloro-4-ethoxy-N-(pyrrolidin-3-yl)pyrimidin-2-amine HCl salt (437 mg, 1.57 mmol), HATU (597 mg, 1.57 mmol) and DIEA (845 mg, 6.55 mmol) in DMF (15 mL) was stirred at RT for overnight. The reaction mixture was extracted by EA/H2O (40/100 mL), dried over Na2SO4, filtered, concentrated and the mixture was purified by by silica gel chromatography (PE/EA = 1/1 ~ 0/1) to afford ((R)-3-((5-chloro-4-ethoxypyrimidin-2-yl)amino)pyrrolidin-1-yl)(4-nitro-3-((tetrahydrofuran-3-yl)oxy)phenyl)methanone (600 mg, 96%) as a yellow solid. [M+H] Calc'd for $C_{21}H_{24}ClN_5O_6$, 478.1; Found, 478.1

Step 4: (4-amino-3-((tetrahydrofuran-3-yl)oxy)phenyl)((R)-3-((5-chloro-4-ethoxypyrimidin-2-yl)amino)pyrrolidin-1-yl)methanone



[00587] A mixture of ((R)-3-((5-chloro-4-ethoxypyrimidin-2-yl)amino)pyrrolidin-1-yl)(4-nitro-3-((tetrahydrofuran-3-yl)oxy)phenyl)methanone (600 mg, 1.47 mmol) and Pd/C (150 mg, 10%) in EtOH (20 mL) was stirred at 50°C overnight underc 1atm H_2 atmosphere. The reaction mixture was filtered and concentrated to afford (4-amino-3-((tetrahydrofuran-3-yl)oxy)phenyl)((R)-3-((5-chloro-4-ethoxypyrimidin-2-yl)amino)pyrrolidin-1-yl)methanone (650 mg, 99%) as a yellow solid. [M+H] Calc'd for $C_{21}H_{26}ClN_5O_4$, 448.2; Found, 448.2.

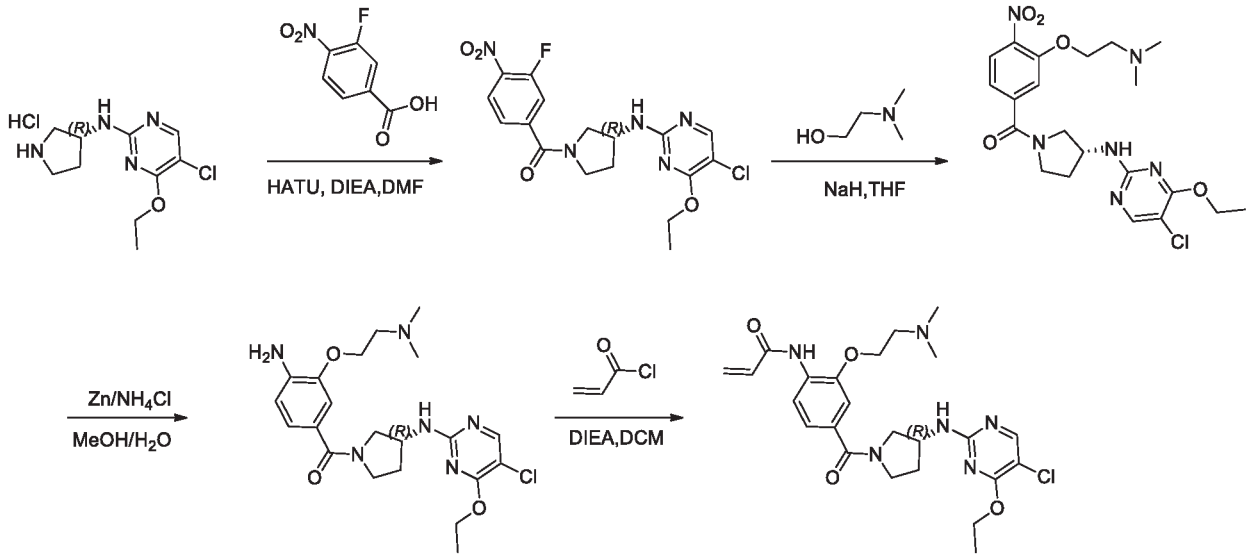
Step 5: N-(4-((R)-3-((5-chloro-4-ethoxypyrimidin-2-yl)amino)pyrrolidine-1-carbonyl)-2-((tetrahydrofuran-3-yl)oxy)phenyl)acrylamide



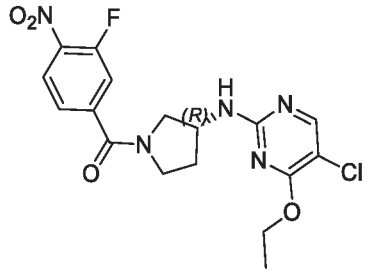
[00588] A mixture of (4-amino-3-((tetrahydrofuran-3-yl)oxy)phenyl)((R)-3-((5-chloro-4-ethoxypyrimidin-2-yl)amino)pyrrolidin-1-yl)methanone (550 mg, 1.23 mmol) and DIEA (238 mg, 1.85 mmol) in DCM (25 mL) was stirred at 0°C under nitrogen atmosphere. Acryloyl chloride (78 mg, 0.86 mmol) in DCM (5 mL) was added dropwise and the mixture was warmed to RT and stirred for overnight.

The mixture was concentrated and purified by *prep*-HPLC to afford N-(4-((R)-3-((5-chloro-4-ethoxypyrimidin-2-yl)amino)pyrrolidine-1-carbonyl)-2-((tetrahydrofuran-3-yl)oxy)phenyl)acrylamide (78.7 mg, 13%) as a white solid. ^{1}H NMR (400 MHz, DMSO- d_6): δ 1.25-1.36 (m, 3H), 1.91-2.25 (m, 4H), 3.38-3.67 (m, 3H), 3.72-3.80 (m, 2H), 3.90-3.92 (m, 3H), 4.23-4.41 (m, 3H), 5.06-5.10 (m, 1H), 5.75-5.77 (m, 1H), 6.23-6.28 (m, 1H), 6.68-6.75 (m, 1H), 7.08-7.14 (m, 2H), 7.64 (s, 1H), 8.07-8.16 (m, 2H), 9.20-9.21 (m, 1H). [M+H] Calc'd for $C_{24}H_{28}ClN_5O_5$, 502.2; Found, 502.2.

Example 144: Synthesis of (R)-N-(4-(3-((5-chloro-4-ethoxypyrimidin-2-yl)amino)pyrrolidine-1-carbonyl)-2-(2-(dimethylamino)ethoxy)phenyl)acrylamide

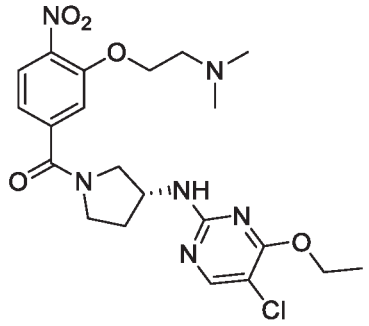


Step 1: (R)-(3-((5-chloro-4-ethoxypyrimidin-2-yl)amino)pyrrolidin-1-yl)(3-fluoro-4-nitrophenyl)methanone



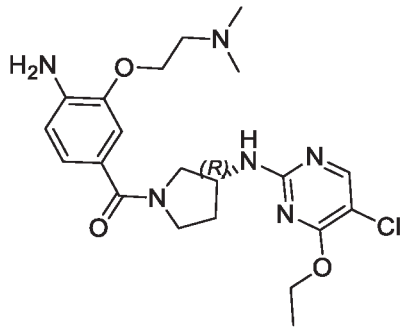
[00589] The title compound was prepared in 86% yield from (*R*)-5-chloro-4-ethoxy-N-(pyrrolidin-3-yl)pyrimidin-2-amine hydrochloride using general procedure of (*R*)-*N*-(4-(3-((5-chloro-4-methylpyrimidin-2-yl)amino)pyrrolidine-1-carbonyl)phenyl)acrylamide. [M+H] Calc'd for $C_{17}H_{17}ClFN_5O_4$, 410.0; Found, 410.0.

Step 2: (R)-(3-((5-chloro-4-ethoxypyrimidin-2-yl)amino)pyrrolidin-1-yl)(3-(2-(dimethylamino)ethoxy)-4-nitrophenyl)methanone



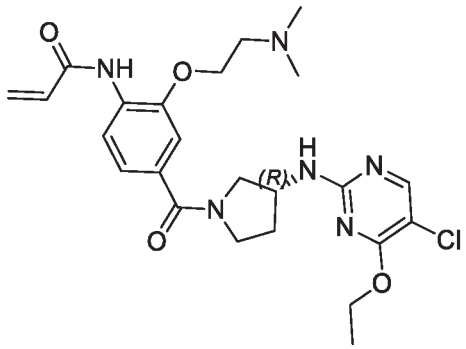
[00590] The title compound was prepared in 64% yield from (*R*)-(3-((5-chloro-4-ethoxypyrimidin-2-yl)amino)pyrrolidin-1-yl)(3-fluoro-4-nitrophenyl)methanone using general procedure of ((R)-3-((5-chloropyrimidin-2-yl)amino)pyrrolidin-1-yl)(4-nitro-3-((tetrahydrofuran-3-yl)oxy)phenyl)methanone. [M+H] Calc'd for $C_{21}H_{27}ClN_6O_5$, 479.1; Found, 479.1.

Step 3: (R)-(4-amino-3-(2-(dimethylamino)ethoxy)phenyl)(3-((5-chloro-4-ethoxypyrimidin-2-yl)amino)pyrrolidin-1-yl)methanone



[00591] The title compound was prepared in 100% yield from (*R*)-(3-((5-chloro-4-ethoxypyrimidin-2-yl)amino)pyrrolidin-1-yl)(3-(2-(dimethylamino)ethoxy)-4-nitrophenyl)methanone using general procedure of (4-amino-3-((tetrahydrofuran-3-yl)oxy)phenyl)((R)-3-((5-chloropyrimidin-2-yl)amino)pyrrolidin-1-yl)methanone. [M+H] Calc'd for $C_{21}H_{29}ClN_6O_3$, 449.1; Found, 449.1.

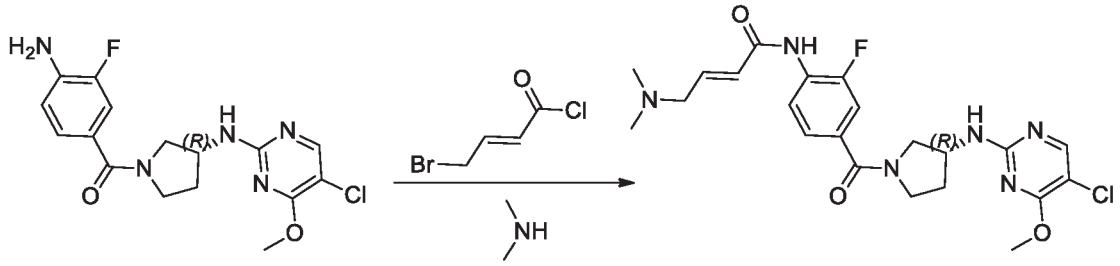
Step 4: (R)-N-(4-(3-((5-chloro-4-ethoxypyrimidin-2-yl)amino)pyrrolidine-1-carbonyl)-2-(2-(dimethylamino)ethoxy)phenyl)acrylamide



[00592] The title compound was prepared in 9% yield from (*R*)-(4-amino-3-(2-(dimethylamino)ethoxy)phenyl)(3-((5-chloro-4-ethoxypyrimidin-2-yl)amino)pyrrolidin-1-yl)methanone using general procedure of (R)-1-(6-(3-((5-chloro-4-methoxypyrimidin-2-

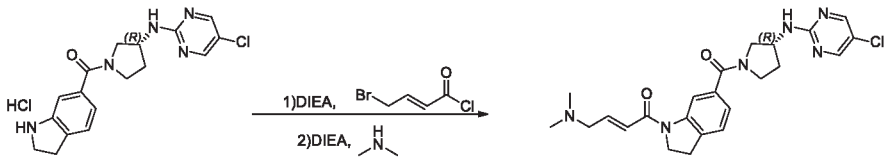
yl)amino)pyrrolidine-1-carbonyl)-2-azaspiro[3.3]heptan-2-yl)prop-2-en-1-one. ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.23-1.36 (m, 3H), 1.89-2.02 (m, 1H), 2.07-2.15 (m, 1H), 2.22 (s, 3H), 2.25 (s, 3H), 2.59-2.63 (m, 2H), 3.39-3.43 (m, 1H), 3.51-3.55 (m, 1H), 3.61-3.65 (m, 1H), 3.74-3.79 (m, 1H), 4.13-4.40 (m, 5H), 5.78 (d, J = 10.4 Hz, 1H), 6.26 (d, J = 16.8 Hz, 1H), 6.52-6.59 (m, 1H), 7.12-7.18 (m, 1H), 7.23 (s, 0.5H), 7.27 (s, 0.5H), 7.64 (brs, 1H), 8.07-8.17 (m, 2H), 9.66 (s, 0.5H), 9.69 (s, 0.5H). [M+H] Calc'd for $C_{24}H_{31}ClN_6O_4$, 503.2; Found, 503.2.

Example 145: Synthesis of (*R*,*E*)-*N*-(4-(3-((5-chloro-4-methoxypyrimidin-2-yl)amino)pyrrolidine-1-carbonyl)-2-fluorophenyl)-4-(dimethylamino)but-2-enamide



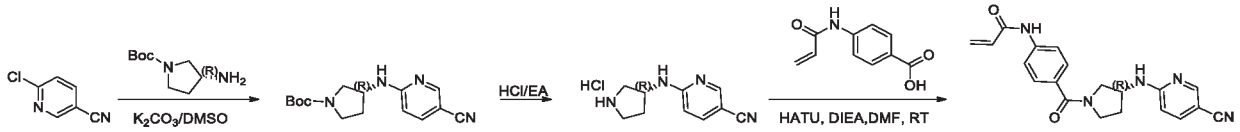
[00593] The title compound was prepared in 6% yield from (R)-(4-amino-3-fluorophenyl)(3-((5-chloro-4-methoxypyrimidin-2-yl)amino)pyrrolidin-1-yl)methanone using general procedure of (*R*,*E*)-1-(8-(3-((5-chloropyrimidin-2-yl)amino)pyrrolidine-1-carbonyl)-2*H*-benzo[b][1,4]oxazin-4(3*H*)-yl)-4-(dimethylamino)but-2-en-1-one. ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.87-2.04 (m, 1H), 2.13-2.17 (m, 7H), 3.06 (d, J = 5.6 Hz, 2H), 3.36-3.48 (m, 1H), 3.51-3.57 (m, 1H), 3.61-3.68 (m, 1H), 3.71-3.79 (m, 1H), 3.86 (s, 1.5H), 3.94 (s, 1.5H), 4.26-4.44 (m, 1H), 6.48 (d, J = 15.2 Hz, 1H), 6.73-6.80 (m, 1H), 7.33-7.45 (m, 2H), 7.68 (brs, 1H), 8.08-8.14 (m, 2H), 9.96 (br s, 1H). [M+H] Calc'd for $C_{22}H_{26}ClFN_6O_3$, 477.1; Found, 477.1.

Example 146: Synthesis of (*R*,*E*)-1-(6-(3-((5-chloropyrimidin-2-yl)amino)pyrrolidine-1-carbonyl)indolin-1-yl)-4-(dimethylamino)but-2-en-1-one

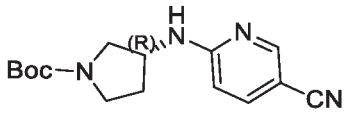


[00594] The title compound was prepared in 21% yield from (*R*)-(3-((5-chloropyrimidin-2-yl)amino)pyrrolidin-1-yl)(indolin-6-yl)methanone hydrochloride using general procedure of (*R*,*E*)-1-(8-(3-((5-chloropyrimidin-2-yl)amino)pyrrolidine-1-carbonyl)-2*H*-benzo[b][1,4]oxazin-4(3*H*)-yl)-4-(dimethylamino)but-2-en-1-one as a trifluroacetate salt. ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.84-2.01 (m, 1H), 2.03-2.22 (m, 1H), 2.81 (s, 6H), 3.20-3.30 (m, 3H), 3.42-3.50 (m, 1H), 3.52-3.58 (m, 1H), 3.61-3.79 (m, 2H), 3.95-3.97 (m, 2H), 4.22-4.44 (m, 2H), 6.72-6.86 (m, 2H), 7.14-7.18 (m, 1H), 7.24-7.33 (m, 1H), 7.80-7.86 (m, 1H), 8.25-8.38 (m, 3H), 9.88 (br s, 1H).

Example 147: Synthesis of (*R*)-*N*-(4-(3-((5-cyanopyridin-2-yl)amino)pyrrolidine-1-carbonyl)phenyl)acrylamide

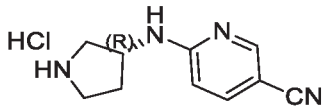


Step 1: (R)-tert-butyl 3-((5-cyanopyridin-2-yl)amino)pyrrolidine-1-carboxylate



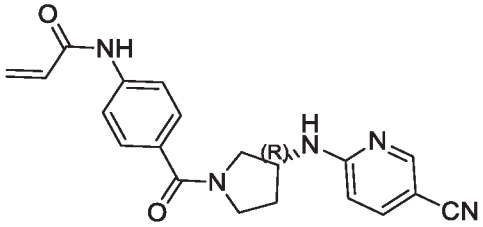
[00595] A mixture of 6-chloronicotinonitrile (900 mg, 6.5 mmol), (*R*)-*tert*-butyl 3-aminopyrrolidine-1-carboxylate (1931 mg, 10.0 mmol) and K_2CO_3 (1791 mg, 13.0 mmol) in DMSO (10 mL) was stirred at 90°C for 2 hours. The mixture was cooled to RT, diluted with water (40 mL) and extracted with EtOAc (30 mL*2). The combined organic phase was washed with brine (30 mL), dried over Na_2SO_4, filtered and concentrated. The residue was purified by flash chromatography on silica gel (petroleum ether/EtOAc = 4/1) to afford (*R*)-*tert*-butyl 3-((5-cyanopyridin-2-yl)amino)pyrrolidine-1-carboxylate (1407 mg, 75%) as a white solid. [M+H] Calc'd for $C_{15}H_{20}N_4O_2$, 289.1; Found, 289.1.

Step 2: (R)-6-(pyrrolidin-3-ylamino)nicotinonitrile hydrochloride



[00596] The title compound was prepared in 100% yield from (*R*)-*tert*-butyl 3-((5-cyanopyridin-2-yl)amino)pyrrolidine-1-carboxylate using general procedure of (*R*)-5-chloro-4-methyl-*N*-(pyrrolidin-3-yl)pyridin-2-amine hydrochloride. [M+H] Calc'd for $C_{10}H_{12}N_4$, 189.1; Found, 189.1.

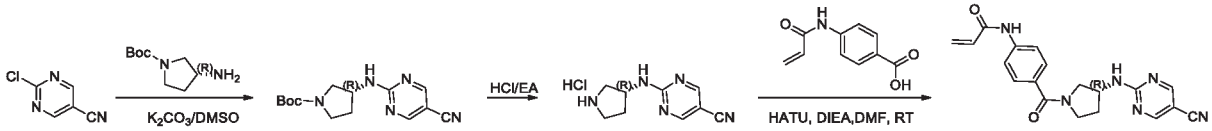
Step 3: (R)-N-(4-(3-((5-cyanopyridin-2-yl)amino)pyrrolidine-1-carbonyl)phenyl)acrylamide



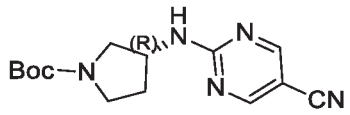
[00597] The title compound was prepared in 32% yield from (*R*)-6-(pyrrolidin-3-ylamino)nicotinonitrile hydrochloride using general procedure of (*R*)-*N*-(4-(3-((5-chloro-4-methylpyrimidin-2-yl)amino)pyrrolidine-1-carbonyl)phenyl)acrylamide. ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.87-1.94 (m, 1H), 2.07-2.23 (m, 1H), 3.43-3.85 (m, 4H), 4.37-4.48 (m, 1H), 5.78 (d, J = 10.8 Hz, 1H), 6.28 (d, J = 16.8 Hz, 1H), 6.41-6.47 (m, 1H), 6.54-6.61 (m, 1H), 7.50-7.54 (m, 2H), 7.66-7.71 (m, 3H),

7.82-7.90 (m, 1H), 8.34 (s, 0.5H), 8.44 (s, 0.5H), 10.30 (s, 1H). [M+H] Calc'd for $C_{20}H_{19}N_5O_2$, 362.1; Found, 362.1.

Example 148: Synthesis of (*R*)-*N*-(4-(3-((5-cyanopyrimidin-2-yl)amino)pyrrolidine-1-carbonyl)phenyl)acrylamide

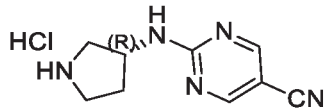


Step 1: (R)-tert-butyl 3-((5-cyanopyrimidin-2-yl)amino)pyrrolidine-1-carboxylate



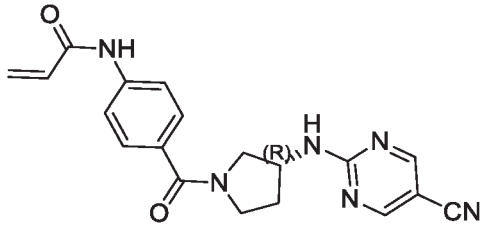
[00598] A mixture of 2-chloropyrimidine-5-carbonitrile (600 mg, 4.3 mmol), (*R*)-*tert*-butyl 3-aminopyrrolidine-1-carboxylate (1287 mg, 6.9 mmol) and K_2CO_3 (1194 mg, 8.6 mmol) in DMSO (5 mL) was stirred at 90°C for 3 hours. The mixture was cooled to RT, diluted with water (30 mL) and extracted with EtOAc (20 mL*2). The combined organic phase was washed with brine (20 mL), dried over Na_2SO_4, filtered and concentrated *in vacuo*. The residue was purified by flash chromatography on silica gel (petroleum ether/EtOAc = 10/1) to afford (*R*)-*tert*-butyl 3-((5-cyanopyrimidin-2-yl)amino)pyrrolidine-1-carboxylate (1.09 g, 88%) as a pink solid. [M+H] Calc'd for $C_{14}H_{19}N_5O_2$, 290.1; Found, 290.1.

Step 2: (R)-2-(pyrrolidin-3-ylamino)pyrimidine-5-carbonitrile hydrochloride



[00599] The title compound was prepared in 100% yield from (*R*)-*tert*-butyl 3-((5-cyanopyrimidin-2-yl)amino)pyrrolidine-1-carboxylate using general procedure of (*R*)-5-chloro-4-methyl-*N*-(pyrrolidin-3-yl)pyridin-2-amine hydrochloride. [M+H] Calc'd for $C_9H_{11}N_5$, 190.1; Found, 190.1.

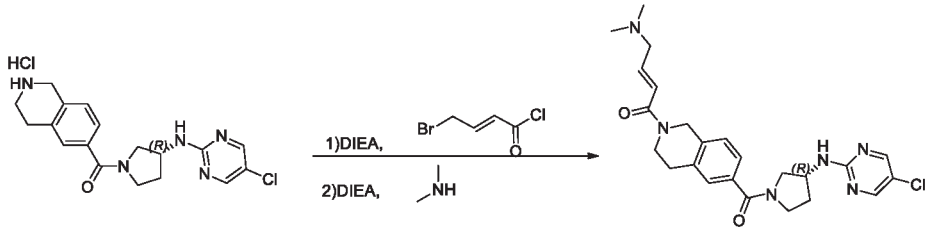
Step 3: (R)-N-(4-(3-((5-cyanopyrimidin-2-yl)amino)pyrrolidine-1-carbonyl)phenyl)acrylamide



[00600] The title compound was prepared in 29% yield from (*R*)-2-(pyrrolidin-3-ylamino)pyrimidine-5-carbonitrile hydrochloride using general procedure of (*R*)-*N*-(4-(3-((5-chloro-4-methylpyrimidin-2-yl)amino)pyrrolidine-1-carbonyl)phenyl)acrylamide. ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.93-2.07 (m, 1H), 2.12-2.21 (m, 1H), 3.36-3.82 (m, 4H), 4.37-4.48 (m, 1H), 5.79 (d, J = 10.0 Hz, 1H), 6.28

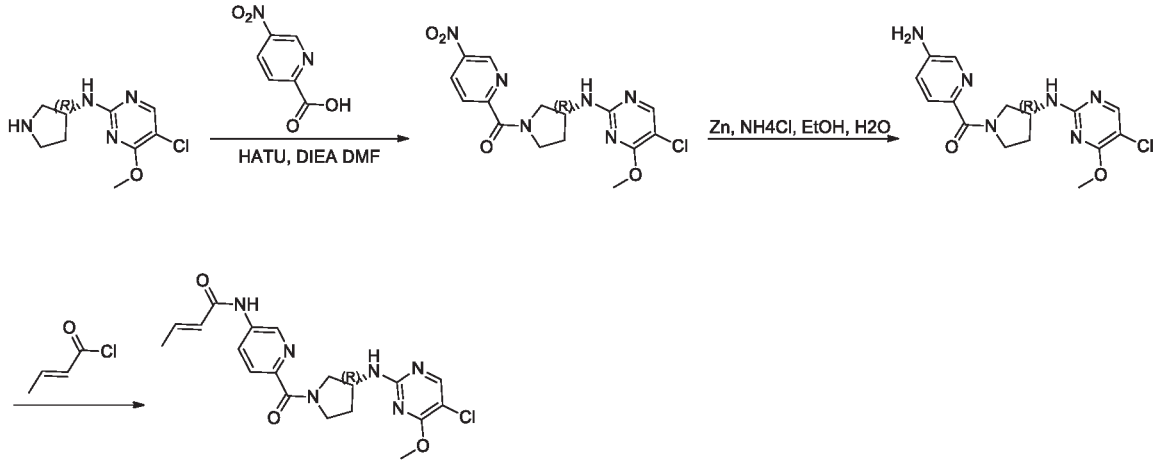
(d, J = 16.8 Hz, 1H), 6.41-6.47 (m, 1H), 7.49-7.54 (m, 2H), 7.68-7.75 (m, 2H), 8.66-8.78 (m, 3H), 10.31 (s, 1H). [M+H] Calc'd for $C_{19}H_{18}N_6O_2$, 363.1; Found, 363.1.

Example 149: Synthesis of (*R*,*E*)-1-(6-(3-((5-chloropyrimidin-2-yl)amino)pyrrolidine-1-carbonyl)-3,4-dihydroisoquinolin-2(1*H*)-yl)-4-(dimethylamino)but-2-en-1-one

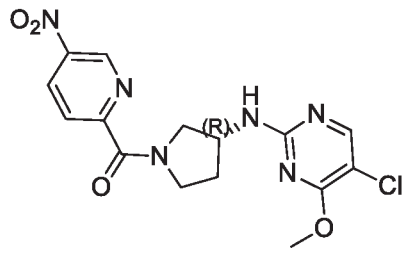


[00601] The title compound was prepared in 19% yield from (*R*)-(3-((5-chloropyrimidin-2-yl)amino)pyrrolidin-1-yl)(1,2,3,4-tetrahydroisoquinolin-6-yl)methanone hydrochloride using general procedure of (*R*,*E*)-1-(8-(3-((5-chloropyrimidin-2-yl)amino)pyrrolidine-1-carbonyl)-2*H*-benzo[b][1,4]oxazin-4(3*H*)-yl)-4-(dimethylamino)but-2-en-1-one. ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.86-2.00 (m, 1H), 2.09-2.15 (m, 1H), 2.18 (s, 6H), 2.81-2.86 (m, 2H), 3.04 (d, J = 3.6 Hz, 2H), 3.40-3.68 (m, 3H), 3.70-3.78 (m, 3H), 4.23-4.40 (m, 1H), 4.67-4.78 (m, 2H), 6.64-6.67 (m, 2H), 7.24-7.35 (m, 3H), 7.78-7.82 (m, 1H), 8.31 (s, 1H), 8.38 (s, 1H). [M+H] Calc'd for $C_{24}H_{29}ClN_6O_2$, 469.2; Found, 469.2.

Example 150: (R,E)-N-(6-(3-((5-chloro-4-methoxypyrimidin-2-yl)amino)pyrrolidine-1-carbonyl)pyridin-3-yl)but-2-enamide

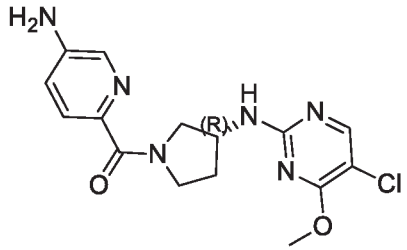


Step 1: (R)-(3-((5-chloro-4-methoxypyrimidin-2-yl)amino)pyrrolidin-1-yl)(5-nitropyridin-2-yl)methanone



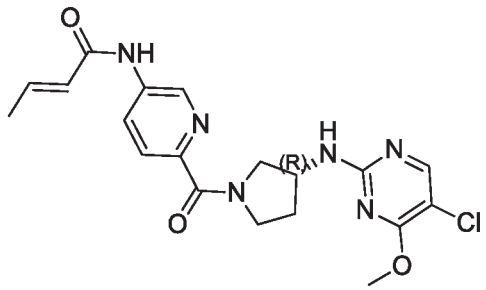
[00602] A mixture of (R)-5-chloro-4-methoxy-N-(pyrrolidin-3-yl)pyrimidin-2-amine (2.2 g, 10.0 mmol), 5-nitropicolinic acid (1.7 g, 10.0 mmol), HATU (3.8 g, 10.0 mmol) and DIEA (3.9 g, 30.0 mmol) in DMF (30 mL) was stirred at RT for overnight. The reaction mixture was concentrated to get the crude product (R)-(3-((5-chloro-4-methoxypyrimidin-2-yl)amino)pyrrolidin-1-yl)(5-nitropyridin-2-yl)methanone (3.4 g, 94%) as a yellow solid. [M+H] MS Calc'd: $C_{15}H_{15}ClN_6O_4$, 379.1; Found: 379.1.

Step 2: (R)-(5-aminopyridin-2-yl)(3-((5-chloro-4-methoxypyrimidin-2-yl)amino)pyrrolidin-1-yl)methanone



[00603] To a solution of (R)-(3-((5-chloro-4-methoxypyrimidin-2-yl)amino)pyrrolidin-1-yl)(5-nitropyridin-2-yl)methanone (3.4 g, 9.0 mmol) in EtOH (150 mL) and H_2O (15 mL) was added Zn (5.9 g, 89.9 mmol) and NH_4Cl (4.8 g, 89.9 mmol). The reaction mixture was stirred at 80°C for 2h. The reaction mixture was concentrated and the residue was purified by column chrography on silica gel to get (R)-(5-aminopyridin-2-yl)(3-((5-chloro-4-methoxypyrimidin-2-yl)amino)pyrrolidin-1-yl)methanone (2.0 g, 68%) as a white solid. [M+H] MS Calc'd: $C_{15}H_{17}ClN_6O_2$, 349.1; Found: 349.1.

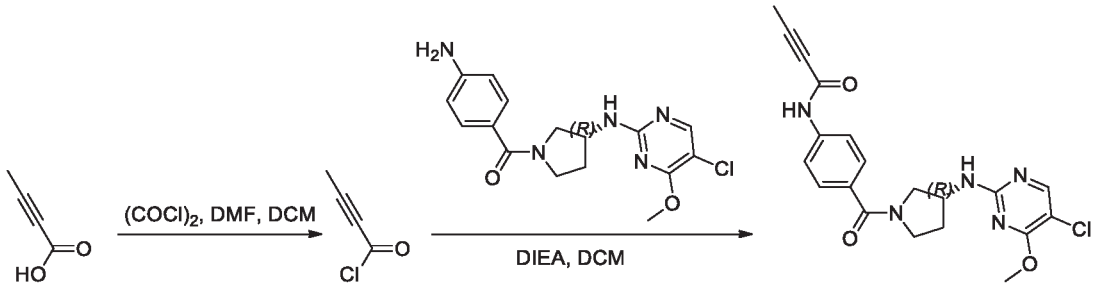
Step 3: (R,E)-N-(6-(3-((5-chloro-4-methoxypyrimidin-2-yl)amino)pyrrolidine-1-carbonyl)pyridin-3-yl)but-2-enamide



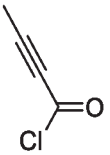
[00604] To a solution of (R)-(5-aminopyridin-2-yl)(3-((5-chloro-4-methoxypyrimidin-2-yl)amino)pyrrolidin-1-yl)methanone (400 mg, 1.15 mmol) and DIEA (450 mg, 3.45 mmol) in DCM (20 mL) and DMF (2 mL) was added (E)-but-2-enoyl chloride (143 mg, 1.38 mmol) at ice-bath. The reaction mixture was stirred at RT for 2h . The reaction mixture was concentrated and the residue was purified by prep-HPLC to afford (R,E)-N-(6-(3-((5-chloro-4-methoxypyrimidin-2-yl)amino)pyrrolidine-1-carbonyl)pyridin-3-yl)but-2-enamide (33.2 mg, 7%) as a white solid. ^1H

NMR (400 MHz, DMSO-d_6): 1.89 (d, J = 6.8 Hz, 3H), 1.96-2.00 (m, 1H), 2.11-2.13 (m, 1H), 3,48-3.80 (m, 3H), 3.88 (s, 3H), 3.93 (s, 1H), 4,75-4,.76 (m, 1H), 6.15-6.16 (s, 1H), 6.84-6.90 (m, 1H), 7.66-7.78 (m, 2H), 8.09-8.19 (m, 2H), 8.77-8.81 (m, 1H), 10.35 (d, J = 5.2 Hz, 1H). [M+H] MS Calc'd: $C_{19}H_{21}ClN_6O_3$,417.1; Found: 417.2.

Example 151: (R)-N-(4-(3-((5-chloro-4-methoxypyrimidin-2-yl)amino)pyrrolidine-1-carbonyl)phenyl)but-2-ynamide

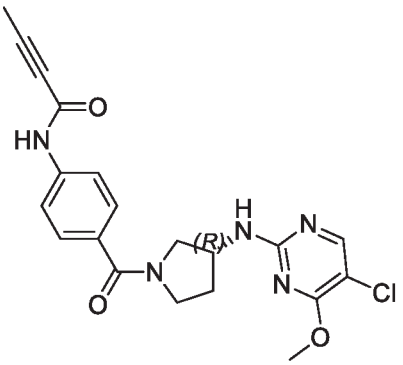


Step 1: but-2-ynoyl chloride



[00605] To a solution of but-2-ynoic acid (800 mg, 9.52 mmol) in DCM (5 mL) was added DMF (1 drop) and $(COCl)_2$ (1.01 g, 9.52 mmol) at 0°C under N_2 atmosphere and allowed to stir at 0°C for 5 min. The crude reaction mixture was used directly in the next step without any additional workup or purification.

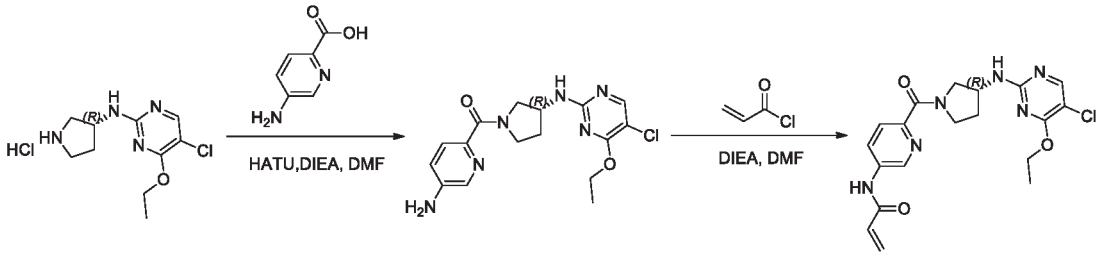
Step 2: (R)-N-(4-(3-((5-chloro-4-methoxypyrimidin-2-yl)amino)pyrrolidine-1-carbonyl)phenyl)but-2-ynamide



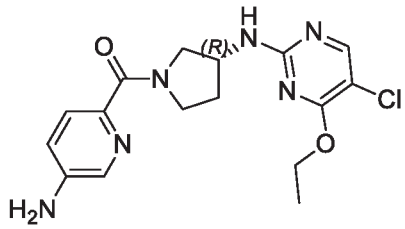
[00606] To a solution of (R)-(4-aminophenyl)(3-((5-chloro-4-methoxypyrimidin-2-yl)amino)pyrrolidin-1-yl)methanone hydrochloride (450 mg, 1.17 mmol) and DIEA (1.23 g, 9.52 mmol) in DCM (15 mL) was added but-2-ynoyl chloride (9.52 mmol) dropwise in an ice-bath. The reaction mixture was stirred at 0°C for 5min. The reaction mixture was concentrated in-vacuo and the residue was purified by prep-HPLC to afford (R)-N-(4-(3-((5-chloro-4-methoxypyrimidin-2-

yl)amino)pyrrolidine-1-carbonyl)phenyl)but-2-ynamide (59.4 mg, 12.2%) as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6): 1.89-2.14 (m, 5H), 3.36-3.79 (m, 4H), 3.86-3.94 (m, 3H), 4.26-4.42 (m, 1H), 7.46-7.65 (m, 5H), 8.07-8.14 (m, 1H), 10.76 (s, 1H). [M+H] MS Calc'd: $C_{20}H_{20}ClN_5O_3$, 414.1; Found: 414.1.

Example 152: Synthesis of (R)-N-(6-(3-((5-chloro-4-ethoxypyrimidin-2-yl)amino)pyrrolidine-1-carbonyl)pyridin-3-yl)acrylamide

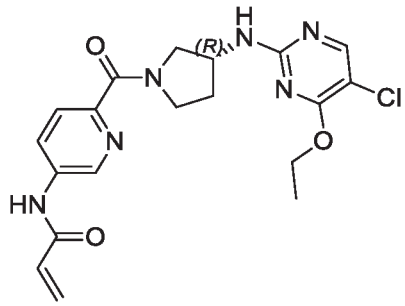


Step 1: (R)-(5-aminopyridin-2-yl)(3-((5-chloro-4-ethoxypyrimidin-2-yl)amino)pyrrolidin-1-yl)methanone



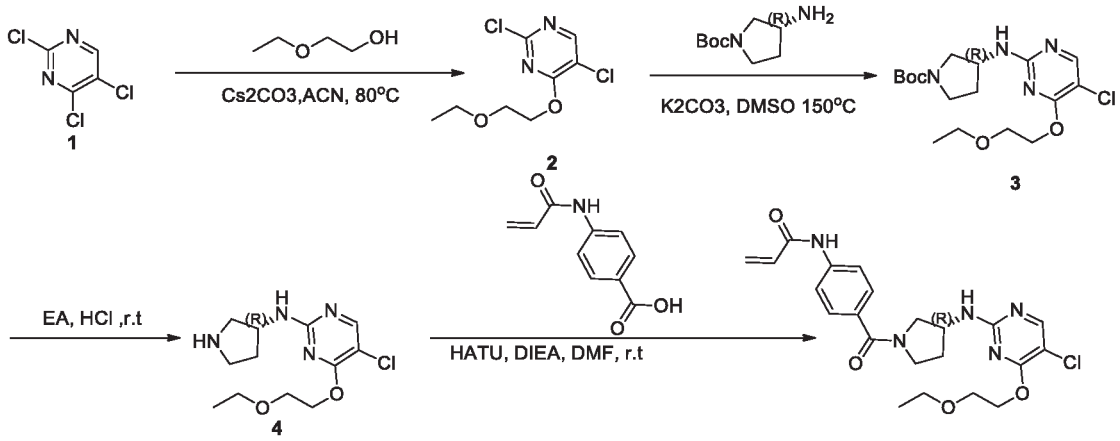
[00607] A mixture of (R)-5-chloro-4-ethoxy-N-(pyrrolidin-3-yl)pyrimidin-2-amine HCl salt (1.63 g, 5.84 mmol), 5-aminopicolinic acid (807 mg, 5.85 mmol), HATU (2.66 g, 7.02 mmol) and DIEA (3.02 g, 23.4 mmol) in DMF (25 mL) was stirred at RT for overnight. To the reaction mixture was added H_2O (150 mL) and extracted with Ethyl Acetate. The combined organic layer was dried over Na_2SO_4, filtered and concentrated. The residue was purified by by silica gel chromatography (DCM/MeOH = 100/1 ~ 20/1) to afford (R)-(5-aminopyridin-2-yl)(3-((5-chloro-4-ethoxypyrimidin-2-yl)amino)pyrrolidin-1-yl)methanone (1.0 g, 48%) as a yellow solid. [M+H] Calc'd for $C_{16}H_{19}ClN_6O_2$, 363.1; Found, 363.1.

Step 2: (R)-N-(6-(3-((5-chloro-4-ethoxypyrimidin-2-yl)amino)pyrrolidine-1-carbonyl)pyridin-3-yl)acrylamide

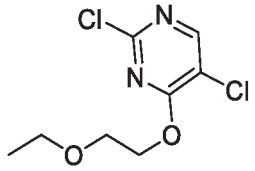


[00608] A mixture of (R)-(5-aminopyridin-2-yl)(3-((5-chloro-4-ethoxypyrimidin-2-yl)amino)pyrrolidin-1-yl)methanone (1.0 g, 2.76 mmol) and DIEA (712 mg, 5.52 mmol) in DMF (30 mL) was stirred at 0°C under nitrogen atmosphere. Acryloyl chloride (275 mg, 3.04 mmol) was added dropwise and the mixture was warmed to RT and stirred for overnight. The mixture was concentrated *in vacuo* and purified by *prep*-HPLC to afford (R)-N-(6-(3-((5-chloro-4-ethoxypyrimidin-2-yl)amino)pyrrolidine-1-carbonyl)pyridin-3-yl)acrylamide (287.8mg, 26%) as a white solid. ^{1}H NMR (400 MHz, DMSO- d_6): δ 1.27-1.36 (m, 3H), 1.94-2.00 (m, 1H), 2.08-2.19 (m, 1H), 3.49-4.05 (m, 4H), 4.30-4.42 (m, 3H), 5.83-5.86 (m, 1H), 6.30-6.35 (m, 1H), 6.42-6.50 (m, 1H), 7.63 (s, 1H), 7.77-7.80 (m, 1H), 8.09-8.23 (m, 2H), 8.80-8.85 (m, 1H), 10.54-10.56 (m, 1H). [M+H] Calc'd for $C_{19}H_{21}ClN_6O_3$, 417.1; Found, 417.1.

Example 153: (R)-N-(4-(3-((5-chloro-4-(2-ethoxyethoxy)pyrimidin-2-yl)amino)pyrrolidine-1-carbonyl)phenyl)acrylamide

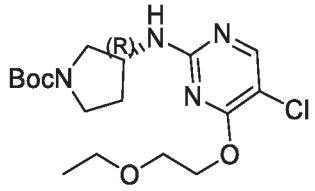


Step 1: 2,5-dichloro-4-(2-ethoxyethoxy)pyrimidine



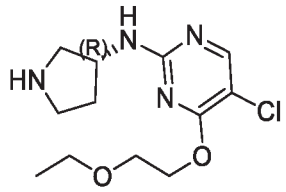
[00609] To a solution of 2,4,5-trichloropyrimidine (2.5 g, 13.7 mmol) and 2-ethoxyethanol (1.1 g, 12.3 mmol) in CH_3CN (40 mL) was added Cs_2CO_3 (6.6 g, 20.5 mmol) at RT. The reaction mixture was stirred at 80°C for 4h. The mixture was cooled, diluted with water (200 mL) and extracted with Ethyl Acetate (100 mL). The combined organic layer was washed with brine (100 mL), dried over Na_2SO_4 filtered and evaporated . The residue was purified by column chromatography to afford 1.8 g of product as a off white solid. [M+H] Calc'd for $C_8H_{10}Cl_2N_2O_2$, 237.1; Found, 237.1.

Step 2: (R)-tert-butyl 3-((5-chloro-4-(2-ethoxyethoxy)pyrimidin-2-yl)amino)pyrrolidine-1-carboxylate



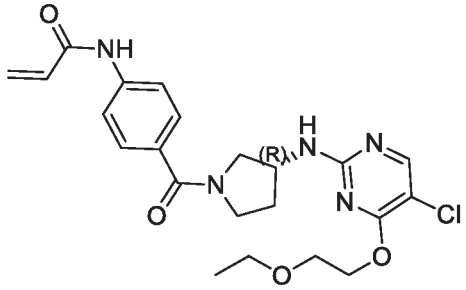
[00610] To a solution of 2,5-dichloro-4-(2-ethoxyethoxy)pyrimidine (1.8 g, 7.6 mmol) and (R)-tert-butyl 3-aminopyrrolidine-1-carboxylate (2.8 g, 15.3 mmol) in DMSO (25 mL) was added K_2CO_3 (2.1 g, 15.3 mmol) at RT. The reaction mixture was stirred at 150°C for 4 h. The reaction mixture was cooled, added water and extracted with Ethyl Acetate. The combined organic layer was washed with brine (100 mL), dried over Na_2SO_4, filtered and concentrated *in vacuo*. The residue was purified by column chromatography to afford 1.8 g crude product as colorless oil. [M+H] Calc'd for $C_{17}H_{27}ClN_4O_4$, 387.1; Found, 387.1.

Step 3: (R)-5-chloro-4-(2-ethoxyethoxy)-N-(pyrrolidin-3-yl)pyrimidin-2-amine



[00611] To a solution of (R)-tert-butyl 3-((5-chloro-4-(2-ethoxyethoxy)pyrimidin-2-yl)amino)pyrrolidine-1-carboxylate (1.8 g, 4.66 mmol) in Ethyl Acetate (20 mL) was bubbled HCl (gas) at -50°C. The reaction mixture was stirred at RT for 3h. The mixture was concentrated *in vacuo* to afford 1.5 g crude product as a yellow solid. [M+H] Calc'd for $C_{12}H_{19}ClN_4O_2$, 287.1; Found, 287.1

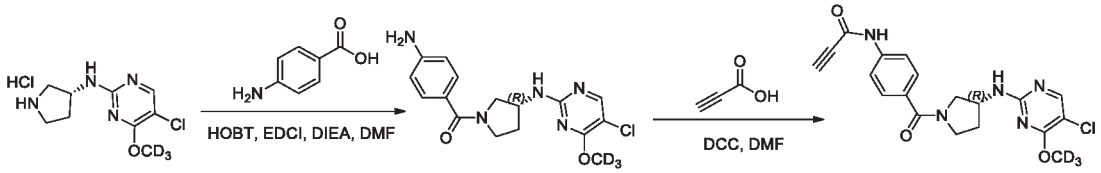
Step 4: (R)-N-(4-(3-((5-chloro-4-(2-ethoxyethoxy)pyrimidin-2-yl)amino)pyrrolidine-1-carbonyl)phenyl)acrylamide



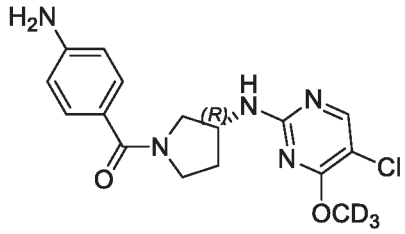
[00612] To a solution of (R)-5-chloro-4-(2-ethoxyethoxy)-N-(pyrrolidin-3-yl)pyrimidin-2-amine (150 mg, 0.5 mmol) and 4-acrylamidobenzoic acid (100 mg, 0.5 mmol) in DMF (3 ml) was added HATU (228 mg, 0.6 mmol) and DIEA (193 mg, 1.5 mmol) at RT. The reaction mixture was stirred at RT for 2h. The reaction mixture was concentrated *in vacuo*. The residue was purified by *prep*-HPLC to afford (R)-N-(4-(3-((5-chloro-4-(2-ethoxyethoxy)pyrimidin-2-yl)amino)pyrrolidine-1-carbonyl)phenyl)acrylamide (17.4 mg, 8%) as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6): 1.05-1.13 (m, 3H), 1.90-2.16 (m, 2H), 3.48-3.71(m, 8H), 4.21-4.47 (m, 3H), 5.77-5.79 (d, J = 10.4 Hz,

1H), 6.25 (s, 0.5H), 6.29 (s, 0.5H), 6.40-6.43 (m, 1H), 7.48-7.53 (m, 2H), 7.69-7.72 (m, 3H), 8.08-8.15 (m, 1H), 10.29 (s, 1H). [M+H] Calc'd for $C_{22}H_{26}ClN_5O_4$, 460.1; Found, 460.1.

Example 154: Synthesis of (R)-N-(4-(3-((5-chloro-4-(trideuteromethoxy)pyrimidin-2-yl)amino)pyrrolidine-1-carbonyl)phenyl)propiolamide

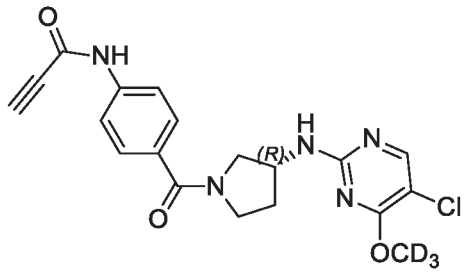


Step 1: (R)-(4-aminophenyl)(3-((5-chloro-4-(trideuteromethoxy)pyrimidin-2-yl)amino)pyrrolidin-1-yl)methanone



[00613] To a solution of (R)-5-chloro-N-(pyrrolidin-3-yl)-4-(trideuteromethoxy)pyrimidin-2-amine hydrochloride (400 mg, 1.49 mmol) and 4-aminobenzoic acid (205 mg, 1.49 mmol) in DMF (6 mL) was added HOBt (349 mg, 2.24 mmol), EDCI (429 mg, 2.24 mmol) and DIEA (577 mg, 4.47 mmol) at ice-bath. The reaction mixture was stirred at RT for 3 hours. After completion of the reaction, the mixture was diluted with water (20 mL) and extracted with EtOAc (20 mL*2). The combined organic layer was washed with brine, dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure. The residue was purified by C18 reversed phase chromatography (20-95% ACN in H_2O) to give (R)-(4-aminophenyl)(3-((5-chloro-4-(trideuteromethoxy)pyrimidin-2-yl)amino)pyrrolidin-1-yl)methanone (310 mg, 59% yield) as a white solid. [M+H] Calc'd : $C_{16}H_{15}D_3ClN_5O_2$, 351.1; Found: 351.1.

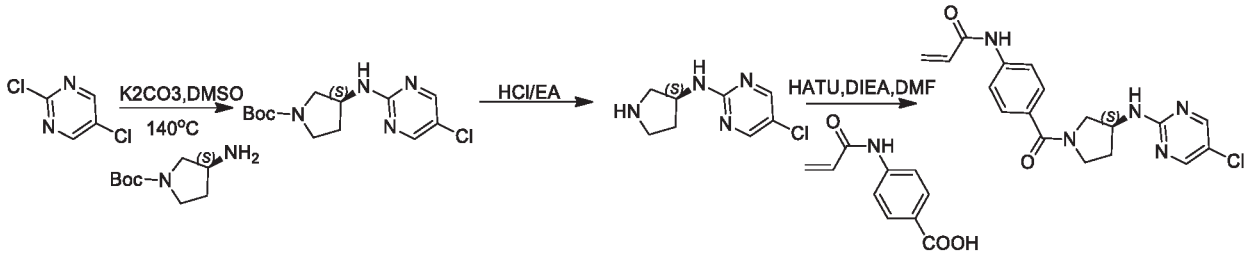
Step 2: (R)-N-(4-(3-((5-chloro-4-(trideuteromethoxy)pyrimidin-2-yl)amino)pyrrolidine-1-carbonyl)phenyl)propiolamide



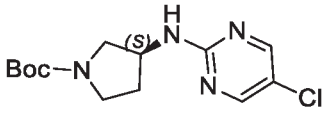
[00614] To a solution of DCC (56 mg, 0.27 mmol) in DMF (2 mL) was added propiolic acid (16 mg, 0.22 mmol) slowly at 0°C under N_2 and the mixture was stirred at 0°C for 1h before the addition of (R)-(4-aminophenyl)(3-((5-chloro-4-(trideuteriomethoxy)pyrimidin-2-yl)amino)pyrrolidin-1-

yl)methanone (65 mg, 0.18 mmol) in DMF (2 mL). The mixture was stirred at 0°C for 1.5h, then warmed to room temperature for overnight. After completion of the reaction, the mixture was diluted with water and the mixture was extracted with DCM (50 mL*2), combined the extracts and washed with brine (50 mL), dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The residue was purified by C18 reversed phase chromatography (20-95% ACN in H_2O) to give (R)-N-(4-(3-((5-chloro-4-(trideuteriomethoxy)pyrimidin-2-yl)amino)pyrrolidine-1-carbonyl)phenyl)propiolamide (5 mg, 7% yield) as pale yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$): 1.98-2.03 (m, 1H), 2.23-2.36 (m, 1H), 2.97 (s, 1H), 3.38-3.41 (m, 0.5H), 3.56-3.90 (m, 3H), 4.00-4.03 (m, 0.5H), 4.44-4.56 (m, 1H), 5.09-5.21 (m, 1H), 7.51-7.56 (m, 4H), 7.86 (s, 1H), 7.97 (s, 0.5H), 8.03 (s, 0.5H). [M+H] Calc'd for $C_{19}H_{15}D_3ClN_5O_3$, 403.1; Found, 403.1.

Example 155: Synthesis of (S)-N-(4-(3-((5-chloropyrimidin-2-yl)amino)pyrrolidine-1-carbonyl)phenyl)acrylamide

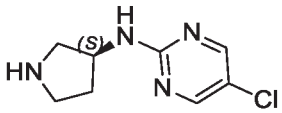


Step 1: (S)-tert-butyl 3-((5-chloropyrimidin-2-yl)amino)pyrrolidine-1-carboxylate



[00615] A mixture of 2,5-dichloropyrimidine (2.0 g, 6.7 mmol), (S)-tert-butyl 3-aminopyrrolidine-1-carboxylate (3.0 g, 8.1 mmol) and K_2CO_3 (3.7 g, 26.8 mmol) in DMSO (20 mL) was stirred at 140°C for 4h. The reaction mixture was cooled, added H_2O (100 mL) and extracted with Ethyl Acetate (100 mL*2), washed with brine (100 mL), dried over Na_2SO_4, filtered and concentrated. The residue was purified by silica gel chromatography (PE/EA = 1/5 to 1/3) to afford (S)-tert-butyl 3-((5-chloropyrimidin-2-yl)amino)pyrrolidine-1-carboxylate (2.5 g, 63%) as a yellow solid. [M+H] Calc'd for $C_{13}H_{19}ClN_4O_2$, 299.1; Found, 299.1.

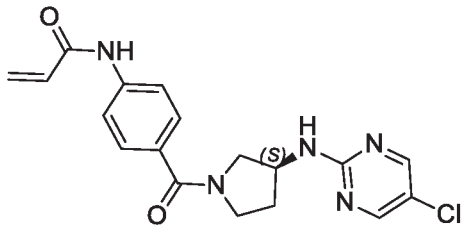
Step 2: (S)-5-chloro-N-(pyrrolidin-3-yl)pyrimidin-2-amine



[00616] A mixture of (S)-tert-butyl 3-((5-chloropyrimidin-2-yl)amino)pyrrolidine-1-carboxylate (2.5 g, 84 mmol) in HCl/EA (10 mL) was stirred at RT for 1h. The reaction mixture was concentrated to

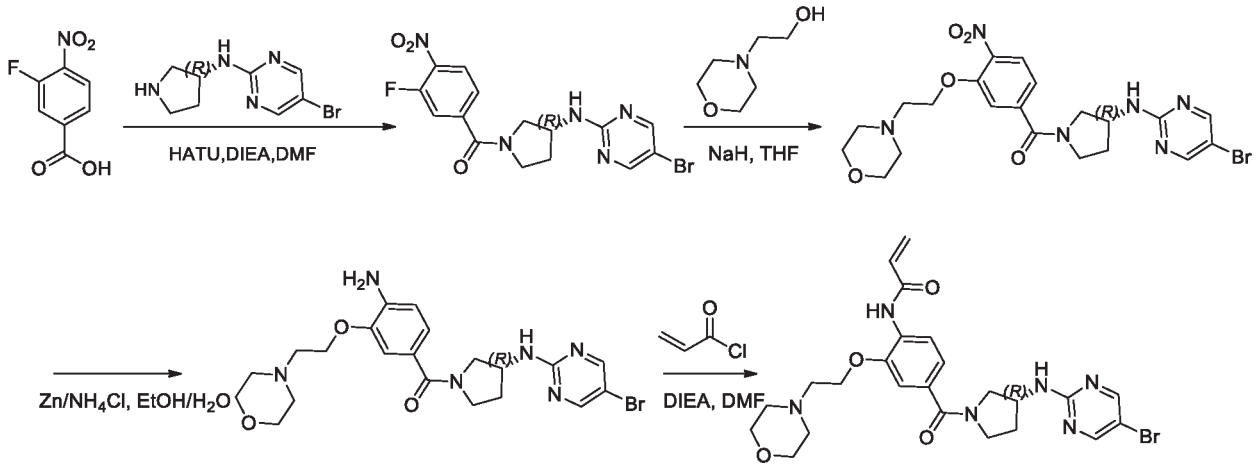
afford (S)-5-chloro-N-(pyrrolidin-3-yl)pyrimidin-2-amine (2.5 g, 100%) as a yellow solid. [M+H] Calc'd for $C_8H_{11}ClN_4$, 199.1; Found, 199.1

Step 3: (S)-N-(4-(3-((5-chloropyrimidin-2-yl)amino)pyrrolidine-1-carbonyl) phenyl)acryl amide

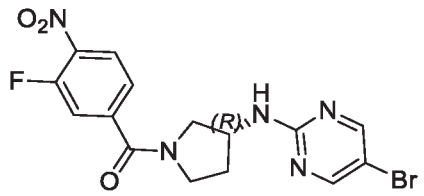


[00617] A mixture of (S)-5-chloro-N-(pyrrolidin-3-yl)pyrimidin-2-amine (700 mg, 3.7 mmol), 4-acrylamidobenzoic acid (802 mg, 4.0 mmol), HATU (1.39 g, 3.7 mmol) and DIEA (946 mg, 7.3 mmol) in DMF (25 mL) was stirred at RT for 4h. To this reaction mixture was added H_2O (100 mL) and extracted with EA (100 mL*2), washed with brine (100 mL). The organic layer was dried over Na_2SO_4, filtered and concentrated. The residue was purified by prep-HPLC to afford (S)-N-(4-(3-((5-chloropyrimidin-2-yl)amino)pyrrolidine-1-carbonyl)phenyl)acrylamide (358 mg, 27%) as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6): 1.90-1.99 (m, 1H), 2.12-2.17 (m, 1H), 3.28-3.82 (m, 4H), 4.24-4.39 (m, 1H), 5.76-5.79 (d, J = 11.2 Hz, 1H), 6.25-6.30 (d, J = 16.8 Hz, 1H), 6.41-6.47 (m, 1H), 7.48-7.53 (m, 2H), 7.68-7.72 (m, 2H), 7.79-7.83 (m, 1H), 8.31 (s, 1H), 8.38 (s, 1H), 10.29 (s, 1H). [M+H] Calc'd for $C_{18}H_{18}ClN_5O_2$, 372.1; Found, 372.1.

Example 156: Synthesis of (R)-N-(4-(3-((5-bromopyrimidin-2-yl)amino)pyrrolidine-1-carbonyl)-2-(2-morpholinoethoxy)phenyl)acrylamide

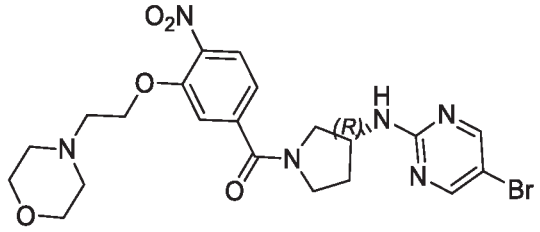


Step 1: (R)-(3-((5-bromopyrimidin-2-yl)amino)pyrrolidin-1-yl)(3-fluoro-4-nitrophenyl)methanone



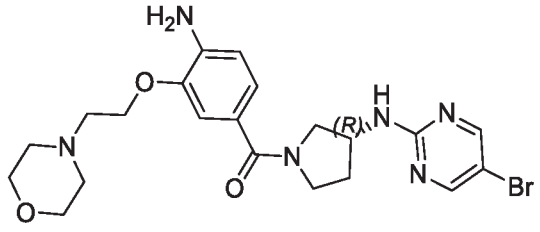
[00618] A mixture of 3-fluoro-4-nitrobenzoic acid (5.0 g, 27.0 mmol), (R)-5-bromo-N-(pyrrolidin-3-yl)pyrimidin-2-amine (7.8 g, 32.4 mml), HATU (15.4 g, 40 mmol) and DIEA (7.0 g, 54 mmol) in DMF (70 mL) was stirred at RT for 16 hrs. The mixture was diluted with H_2O (100 mL) and extracted with EA (200 mL*2). The combined organic layer was dried over Na_2SO_4, filtered and concentrated. The residue was purified by silica gel chromatograpgy to give (R)-(3-((5-bromopyrimidin-2-yl)amino)pyrrolidin-1-yl)(3-fluoro-4-nitrophenyl)methanone (7.0 g, 64%) as yellow oil. [M+H] Calc'd for $C_{15}H_{13}BrFN_5O_3$, 410.0; Found, 410.0.

Step 2: (R)-(3-((5-bromopyrimidin-2-yl)amino)pyrrolidin-1-yl)(3-(2-morpholinoethoxy)-4-nitrophenyl)methanone



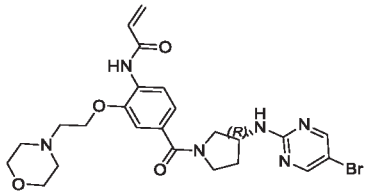
[00619] A mixture of 2-morpholinoethanol (192 mg, 1.5 mmol) in THF (20 mL) was stirred at 0°C. NaH (132 mg, 3.4 mmol, 60%) was added. The reaction mixture was stirred at RT for 20 min and then (R)-(3-((5-bromopyrimidin-2-yl)amino)pyrrolidin-1-yl)(3-fluoro-4-nitrophenyl)methanone (600 mg, 1.5 mmol) was added. The reaction mixture was then stirred at RT overnight. The mixture was diluted with water (20 mL) and extracted with EA (20 mL* 3). The combined organic layer was washed with brine (20 mL), dried over Na_2SO_4, filtered and concentrated and purified by silica gel chromatography to afford (R)-(3-((5-bromopyrimidin-2-yl)amino)pyrrolidin-1-yl)(3-(2-morpholinoethoxy)-4-nitrophenyl)methanone (466 mg, 60%) as yellow solid. [M+H] Calc'd for $C_{21}H_{25}BrN_6O_5$, 521.1; Found, 521.1

Step 3: (R)-(4-amino-3-(2-morpholinoethoxy)phenyl)(3-((5-bromopyrimidin-2-yl)amino)pyrrolidin-1-yl)methanone



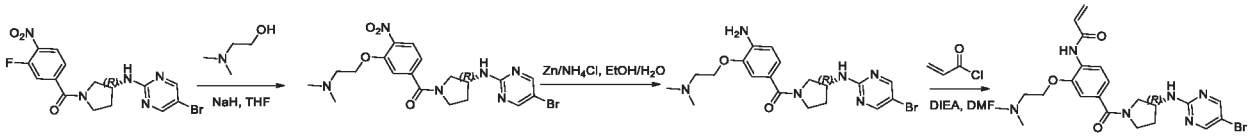
[00620] A mixture of (R)-(3-((5-bromopyrimidin-2-yl)amino)pyrrolidin-1-yl)(3-(2-morpholinoethoxy)-4-nitrophenyl)methanone (260 mg, 0.5 mmol) and NH_4Cl (268 mg, 5.0 mmol) in $MeOH/H_2O$ (10 mL/2 mL) was stirred at 50°C for 1h. Zn (325 mg, 5 mmol) was added to the mixture at RT and then warmed to 70°C for 3h. The mixture was filtered and concentrated to afford (R)-(4-amino-3-(2-morpholinoethoxy)phenyl)(3-((5-bromopyrimidin-2-yl)amino)pyrrolidin-1-yl)methanone (200 mg, 84%) as a yellow solid. [M+H] Calc'd for $C_{21}H_{27}BrN_6O_3$, 491.1; Found, 491.1.

Step 4: (R)-N-(4-(3-((5-bromopyrimidin-2-yl)amino)pyrrolidine-1-carbonyl)-2-(2-morpholinoethoxy)phenyl)acrylamide

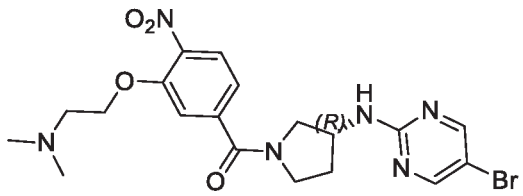


[00621] A mixture of (R)-(4-amino-3-(2-morpholinoethoxy)phenyl)(3-((5-bromopyrimidin-2-yl)amino)pyrrolidin-1-yl)methanone (200 mg, 0.41 mmol) and DIEA (129 mg, 1 mmol) in DCM (10 mL) was stirred at 0°C under nitrogen atmosphere. Acryloyl chloride (37 mg, 0.41 mmol) was added dropwise and the mixture was warmed to RT and stirred for 1h. The mixture was concentrated and purified by *prep*-HPLC to afford (R)-N-(4-(3-((5-bromopyrimidin-2-yl)amino)pyrrolidine-1-carbonyl)-2-(2-morpholinoethoxy)phenyl)acrylamide (129.7 mg, 58%) as a white solid. 1H NMR (400 MHz, DMSO-d_6): δ 1.90-2.16 (m, 2H), 2.44-2.51 (m, 4H), 2.70-2.76 (m, 2H), 3.34-3.37 (m, 1H), 3.54-3.55 (m, 5H), 3.64-3.77 (m, 2H), 4.18-4.39 (m, 3H), 5.75-5.78 (m, 1H), 6.23-6.27 (m, 1H), 6.62-6.65 (m, 1H), 7.10-7.24 (m, 2H), 7.80-8.08 (m, 2H), 8.36-8.42 (m, 1H), 9.26 (s, 1H). [M+H] Calc'd for $C_{24}H_{29}BrN_6O_4$, 545.1; Found, 545.1.

Example 157: Synthesis of (R)-N-(4-(3-((5-chloropyrimidin-2-yl)amino)pyrrolidin-1-yl)quinazolin-7-yl)acrylamide



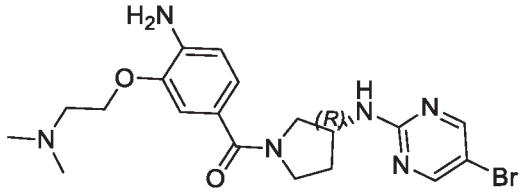
Step 1: (R)-(3-((5-bromopyrimidin-2-yl)amino)pyrrolidin-1-yl)(3-(2-(dimethylamino)ethoxy) -4-nitrophenyl)methanone



[00622] To a mixture of 2-(dimethylamino)ethanol (174 mg, 1.9 mmol) in THF (60 mL) was added NaH (156 mg, 3.9 mmol, 60%) at 0°C and the reaction mixture was stirred at 0°C for 15 min. Then

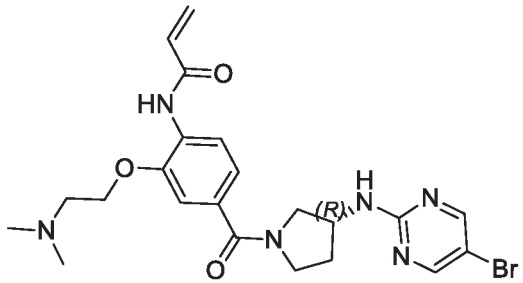
added (R)-(3-((5-bromopyrimidin-2-yl)amino)pyrrolidin-1-yl)(3-fluoro-4-nitrophenyl)methanone (800 mg, 1.9 mmol) to the mixture and stirred at RT for overnight. The reaction was quenched with H_2O (10 mL) and the mixture was concentrated. The residue was purified by silica gel chromatography (DCM/MeOH = 20/1) to afford (R)-(3-((5-bromopyrimidin-2-yl)amino)pyrrolidin-1-yl)(3-(2-(dimethylamino)ethoxy)-4-nitrophenyl)meth anone (700 mg, 75%) as a yellow solid. [M+H] Calc'd for $C_{19}H_{23}BrN_6O_4$, 479.1; Found, 479.1.

Step 2: (R)-(4-amino-3-(2-(dimethylamino)ethoxy)phenyl)(3-((5-bromopyrimidin-2-yl)amino)pyrrolidin-1-yl)methanone



[00623] To a mixture of (R)-(3-((5-bromopyrimidin-2-yl)amino)pyrrolidin-1-yl)(3-(2-(dim ethylamino)et hoxy)-4-nitrophenyl)meth anone (700 mg, 1.5 mmol) in MeOH/H_2O (20 /5 mL) was added NH_4Cl (791 mg, 0.15 mmol) and Zn (952 mg, 0.15 mmol). The reaction mixture was stirred at 70°C for 2h. The mixture was cooled, fitered and concentrated *in vacuo*. The residue was purified by silica gel chromatography (DCM/MeOH = 20/1) to afford (R)-(4-amino-3-(2-(dimethylamino)ethoxy)phenyl)(3-((5-bromopyrimidin-2-yl)amino)pyr rolidin-1-yl)methanone (400 mg, 61%) as yellow solid. [M+H] Calc'd for $C_{19}H_{25}BrN_6O_2$, 449.1; Found, 449.1.

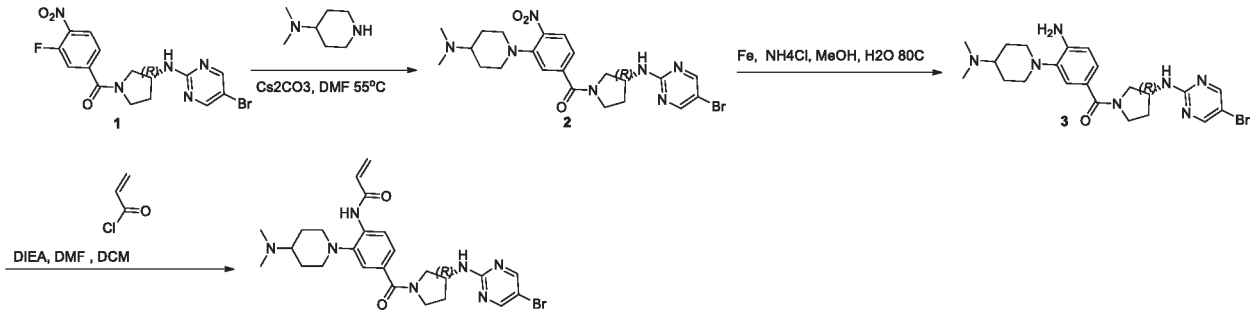
Step 3: (R)-N-(4-(3-((5-bromopyrimidin-2-yl)amino)pyrrolidine-1-carbonyl)-2-(2-(dimethylamino)ethoxy)phenyl)acrylamide



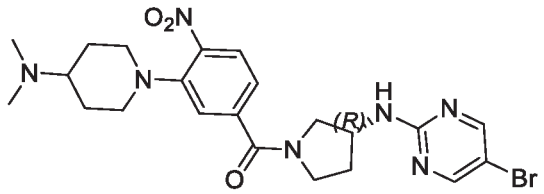
[00624] A mixture of (R)-(4-amino-3-(2-(dimethylamino)ethoxy)phenyl)(3-((5-bromopyrimidin-2-yl)amino)pyrrolidin-1-yl)methanone (400 mg, 1.5 mmol) in DCM (20/5 mL) was added DIEA (230 mg, 1.8 mmol) and Acryloyl chloride (81 mg, 0.89 mmol) in an ice-bath. The reaction was then allowed to warm and stirred at RT for 2 h. The mixture was concentrated *in vacuo* and purified by prep-HPLC to afford (R)-N-(4-(3-((5-bromopyrimidin-2-yl)amino)pyrrolidine-1-carbonyl)-2-(2-(dimethylamino)ethoxy)phenyl)acrylamide (66.9 mg, 15%) as white solid. ^1H NMR (400 MHz, DMSO-d_6): 1.89-1.99 (m, 1H), 2.15-2.22 (m, 1H), 2.23 (d, J = 8.4 Hz, 6H), 2.60-2.63 (m, 2H), 3.35-3.44 (m, 1H), 3.52-3.56 (m, 1H), 3.63-3.67 (m, 1H), 3.74-3.78 (m, 1H), 4.12-4.18 (m, 2H),

4.21-4.40 (m, 1H), 5.78 (d, J = 10.0 Hz, 1H), 6.24-6.28 (m, 6H), 6.52-6.58 (m, 1H), 7.12-7.17 (m, 1H), 7.23-7.27 (m, 1H), 7.80 (d, J = 4.8 Hz, 1H), 8.12-8.17 (m, 1H), 8.36 (s, 1H), 8.42 (s, 1H), 9.66 (d, J = 12.4 Hz, 1H). [M+H] Calc'd for $C_{22}H_{27}BrN_6O_3$, 503.1; Found, 503.1.

Example 158: (R)-N-(4-(3-((5-bromopyrimidin-2-yl)amino)pyrrolidine-1-carbonyl)-2-(4-(dimethylamino)piperidin-1-yl)phenyl)acrylamide

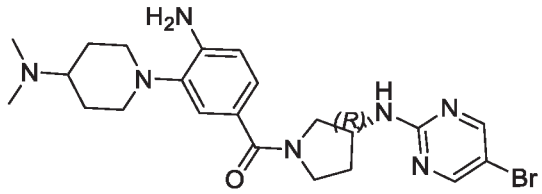


Step 1:(R)-(3-((5-bromopyrimidin-2-yl)amino)pyrrolidin-1-yl)(3-(4-(dimethylamino)piperidin-1-yl)-4-nitrophenyl)methanone



[00625] To a solution of (R)-(3-((5-bromopyrimidin-2-yl)amino)pyrrolidin-1-yl)(3-fluoro-4-nitrophenyl)methanone (1.0 g, 2.5 mmol) and N,N-dimethylpiperidin-4-amin (320 mg, 2.5 mmol) in DMF (50 mL) was added Cs_2CO_3 (3.3 g,10 mmol) at RT. The mixture was then stirred at 55°C for 2h. The mixture was cooled, diluted with water (200 mL) and extracted with EA (100 mL). The organic layer was washed with brine (100 mL), dried over Na_2SO_4, filtered and concentrated to afford 1.0 g of product as a yellow solid. [M+H] Calc'd for $C_{22}H_{28}BrN_7O_3$, 518.1; Found, 518.1

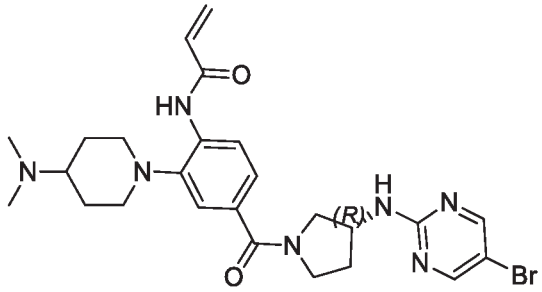
Step 2:(R)-(4-amino-3-(4-(dimethylamino)piperidin-1-yl)phenyl)(3-((5-bromopyrimidin-2-yl)amino)pyrrolidin-1-yl)methanone



[00626] To a solution of (R)-(3-((5-bromopyrimidin-2-yl)amino)pyrrolidin-1-yl)(3-(4-(dimethylamino)piperidin-1-yl)-4-nitrophenyl)methanone (1.0 g，2.0 mmol) in ethanol (40 mL) and water (40 mL) was added Fe (2.2 g, 40.0 mmol) and NH_4Cl (2.1 g, 40.0 mmol) at RT. The mixture was then stirred at 80°C for 2h. The reaction mixture was concentrated *in vacuo*. The

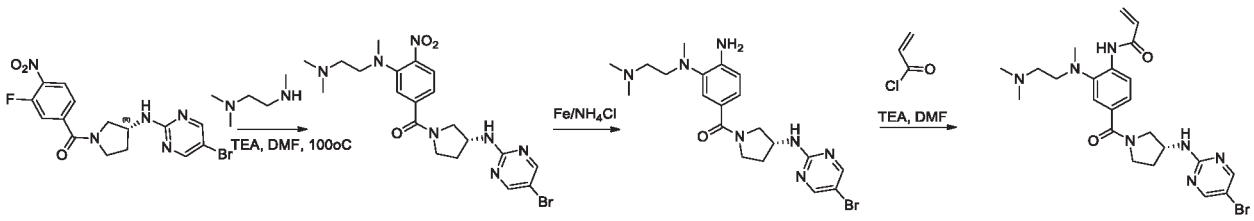
residue was purified by reversed phase chromatography (ACN in water 30%-70%) to afford 500 mg of product as a yellow solid. [M+H] Calc'd for $C_{20}H_{30}N_4O_6$, 488.1; Found, 488.1.

Step 3: (R)-N-(4-(3-((5-bromopyrimidin-2-yl)amino)pyrrolidine-1-carbonyl)-2-(4-(dimethylamino)piperidin-1-yl)phenyl)acrylamide

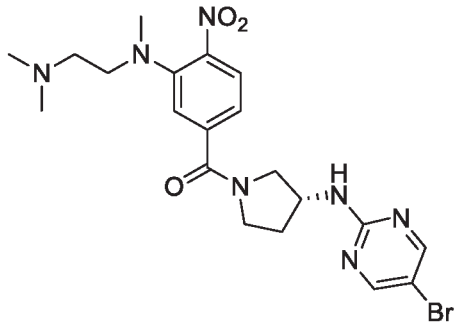


[00627] To a solution of (R)-(4-amino-3-(4-(dimethylamino)piperidin-1-yl)phenyl)(3-((5-bromopyrimidin-2-yl)amino)pyrrolidin-1-yl)methanone (400 mg, 0.82 mmol) and DIEA (210 mg, 1.6 mmol) in DCM (20 mL) and DMF (2 mL) was added acryloyl chloride (81 mg, 0.9 mmol) in an ice-bath. The reaction mixture was then stirred at RT for 2h, The reaction mixture was concentrated *in vacuo* and the residue was purified by *prep*-HPLC to afford (R)-N-(4-(3-((5-bromopyrimidin-2-yl)amino)pyrrolidine-1-carbonyl)-2-(4-(dimethylamino)piperidin-1-yl)phenyl)acrylamide(63.8 mg, 14.5%) as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6): 1.67-1.96 (m, 5H), 2.14-2.21 (m, 8H), 2.54-2.63 (m, 2H), 2.9-3.1 (m, 2H), 3.31-3.65 (m, 4H), 4.22 (s, 0.5H), 4.37 (s, 0.5H), 5.77-5.79 (d, J = 10.0 Hz, 1H), 6.24 (s, 0.5H), 6.28 (s, 0.5H), 6.70-6.77 (m,1H), 7.19-7.30 (m, 2H), 7.81-7.82 (d, J = 5.2 Hz, 1H), 8.03-8.04 (m, 1H), 8.36 (s, 1H), 8.42 (s, 1H), 9.09-9.11 (d, J = 8.4 Hz, 1H). [M+H] Calc'd for $C_{25}H_{32}BrN_7O_2$,542.1; Found, 542.1.

Example 159: Synthesis of (R)-N-(4-(3-((5-bromopyrimidin-2-yl)amino)pyrrolidine-1-carbonyl)-2-((2-(dimethylamino)ethyl)(methyl)amino)phenyl)acrylamide

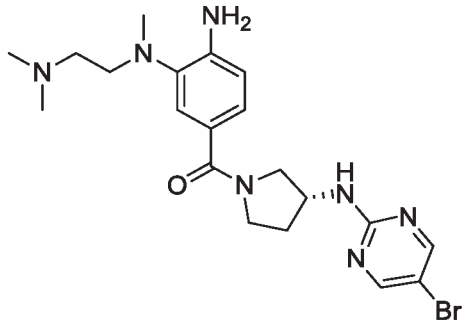


Step 1: (R)-(3-((5-bromopyrimidin-2-yl)amino)pyrrolidin-1-yl)(3-((2-(dimethylamino)ethyl)(methyl)amino)-4-nitrophenyl)methanone



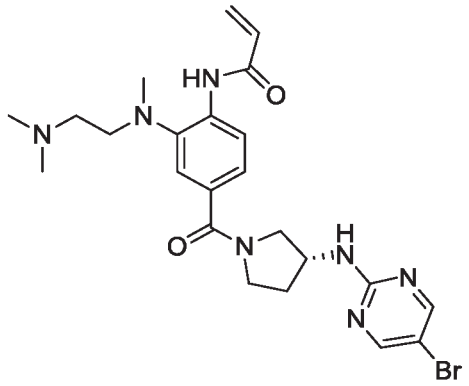
[00628] A mixture of (R)-(3-((5-bromopyrimidin-2-yl)amino)pyrrolidin-1-yl)(3-fluoro-4-nitrophenyl)methanone (1.0 g, 2.44 mmol), N1,N1,N2-trimethylethane-1,2-diamine (324 mg, 3.18 mmol) and TEA (985 mg, 9.76 mmol) in DMF (10 mL) was stirred at 100°C for 16h. The solution was concentrated and purified by silica gel chromatography (DCM/MeOH = 7/1) to afford (R)-(3-((5-bromopyrimidin-2-yl)amino)pyrrolidin-1-yl)(3-((2-(dimethylamino)ethyl)(methyl)amino)-4-nitrophenyl)methanone (666 mg, 56%) as brown glutinous oil. [M+H] Calc'd for $C_{20}H_{26}BrN_7O_3$, 492.1, Found, 492.3

Step 2: (R)-(4-amino-3-((2-(dimethylamino)ethyl)(methyl)amino)phenyl)(3-((5-bromo pyrimidin-2-yl)amino)pyrrolidin-1-yl)methanone



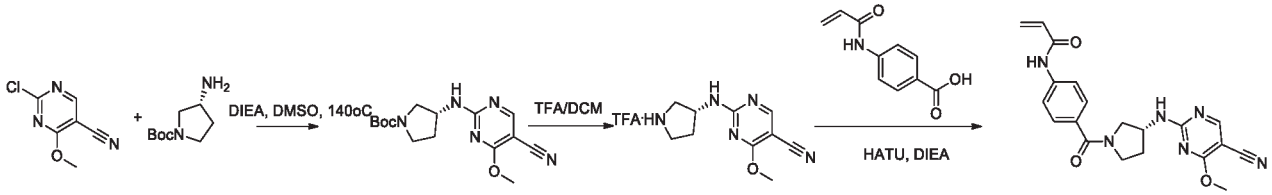
[00629] To a mixture of (R)-(3-((5-bromopyrimidin-2-yl)amino)pyrrolidin-1-yl)(3-((2-(dimethylamino)ethyl)(methyl)amino)-4-nitrophenyl)methanone (500 mg, 0.84 mmol) in EtOH/H_2O (10/10 mL) was added NH_4Cl (454 mg, 8.4 mmol) and Fe (467 mg, 8.4 mmol) at RT. The reaction mixture was stirred at 80°C for 5 h. The mixture was fitered and concentrated. The residue was purified by silica gel chromatography (DCM/MeOH = 7/1) to afford (R)-(4-amino-3-((2-(dimethylamino)ethyl)(methyl)amino)phenyl)(3-((5-bromopyrimidin-2-yl)amino)pyrrolidin-1-yl)methanone (410 mg, 100%) as a brown solid. [M+H] Calc'd for $C_{20}H_{28}BrN_7O$, 462.2; Found, 462.1

Step 3: (R)-N-(4-(3-((5-bromopyrimidin-2-yl)amino)pyrrolidine-1-carbonyl)-2-((2-(dimethyl amino)ethyl)(methyl)amino)phenyl)acrylamide

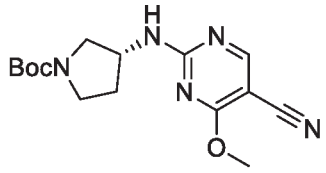


[00630] To a mixture of (R)-(4-amino-3-((2-(dimethylamino)ethyl)(methyl)amino)phenyl)(3-((5-bromopyrimidin-2-yl)amino)pyrrolidin-1-yl)methanone (419 mg, 0.91 mmol) in DMF (5 mL) was added TEA (184 mg, 1.8 mmol) and Acryloyl chloride (73 mg, 0.91 mmol) in an ice-bath. After stirring at RT for 2h, the mixture was concentrated and purified by prep-HPLC to afford (R)-N-(4-(3-((5-bromopyrimidin-2-yl)amino)pyrrolidine-1-carbonyl)-2-((2-(dimethylamino)ethyl)(methyl)amino)phenyl)acrylamide (30 mg, 6%) as white solid. ^{1}H NMR (400 MHz, DMSO-d_6): 1.86-2.02 (m, 1H), 2.17-2.20 (m, 7H), 2.26-2.33 (m, 2H), 2.59-2.70 (m, 3H), 2.78-2.81 (m, 2H), 3.35-3.78 (m, 4H), 4.23-4.40 (m, 1H), 5.81 (d, J = 10.4 Hz, 1H), 6.25-6.45 (m, 2H), 7.25-7.31 (m, 1H), 7.40-7.46 (m, 1H), 7.81 (d, J = 5.6 Hz, 1H), 8.29-8.43 (m, 3H) 10.21-10.26 (m, 1H). [M+H] Calc'd for $C_{23}H_{30}BrN_7O_2$, 516.2; Found, 516.2

Example 160: Synthesis of (R)-N-(4-(3-((5-bromopyrimidin-2-yl)amino)pyrrolidine-1-carbonyl)-2-((2-(dimethylamino)ethyl)(methyl)amino)phenyl)acrylamide

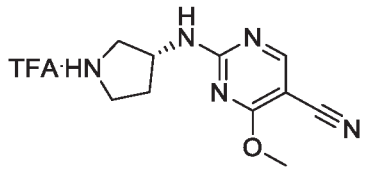


Step 1: (R)-tert-butyl 3-((5-cyano-4-methoxypyrimidin-2-yl)amino)pyrrolidine-1-carboxylate



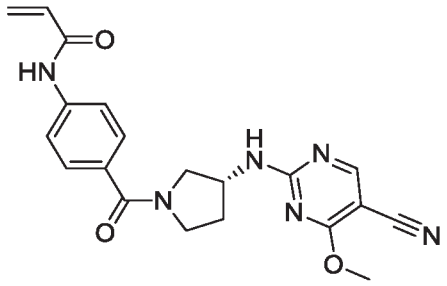
[00631] A mixture of 2,4-dichloropyrimidine-5-carbonitrile (900 mg, 5.33 mmol), (R)-tert-butyl 3-aminopyrrolidine-1-carboxylate (1.24 g, 6.66 mmol) and DIEA (1.38 g, 10.66 mmol) in DMSO (10 mL) was stirred at 140°C for 3h. The reaction was cooled, quenched with H_2O (100 mL) and extracted with DCM (50 mL*2). The combined organic layer was concentrated and purified by silica gel chromatography (PE/EA = 3/1) to afford (R)-tert-butyl 3-((5-cyano-4-methoxypyrimidin-2-yl)amino)pyrrolidine-1-carboxylate (280 mg, 18%) as brown solid. [M+H] Calc'd for $C_{15}H_{21}N_5O_3$, 320.2; Found, 320.3

Step 2: (R)-4-methoxy-2-(pyrrolidin-3-ylamino)pyrimidine-5-carbonitrile 2,2,2-trifluoroacetate



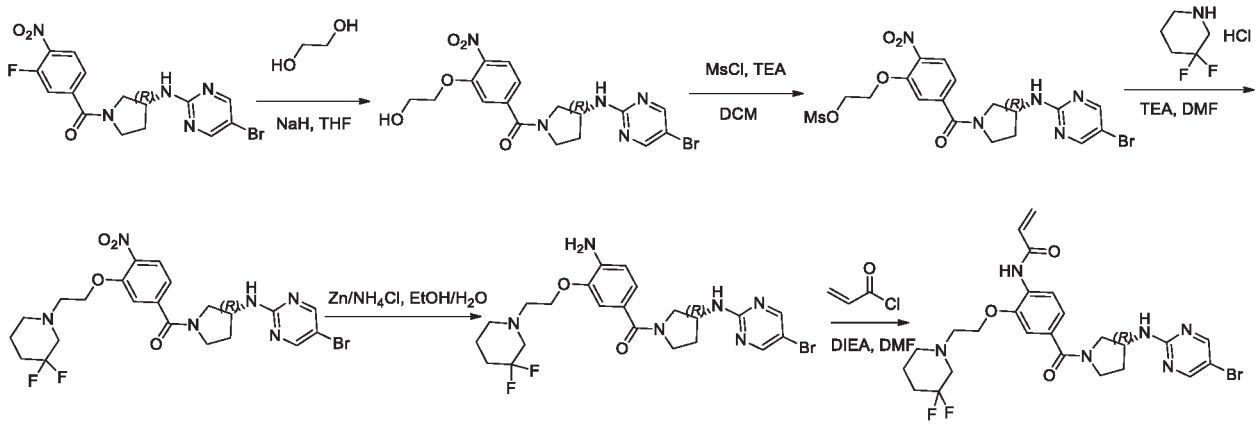
[00632] A mixture of (R)-tert-butyl 3-((5-cyano-4-methoxypyrimidin-2-yl)amino)pyrrolidine-1-carboxylate (98 mg, 0.31 mmol) in DCM/TFA (2/1 mL) was stirred at RT for 30 min. The mixture was concentrated to afford (R)-4-methoxy-2-(pyrrolidin-3-ylamino)pyrimidine-5-carbonitrile 2,2,2-trifluoroacetate (190 mg of crude) as brown glutinous oil. [M+H] Calc'd for $C_{10}H_{14}ClN_5O$, 220.1; Found, 220.1

Step 3: (R)-N-(4-(3-((5-cyano-4-methoxypyrimidin-2-yl)amino)pyrrolidine-1-carbonyl)phenyl)acrylamide

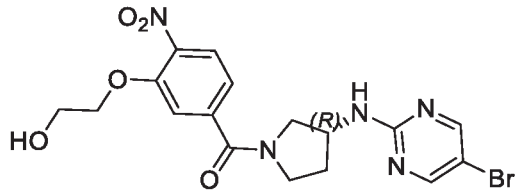


[00633] To a mixture of (R)-4-methoxy-2-(pyrrolidin-3-ylamino)pyrimidine-5-carbonitrile 2,2,2-trifluoroacetate (190 mg, 0.87 mmol), DIEA (337 mg, 2.61 mmol) and HATU (397 mg, 1.04 mmol) in DCM (5 mL) was added 4-acrylamidobenzoic acid (165 mg, 0.87 mmol). After stirring at RT for 1h, the mixture was concentrated and purified by prep-HPLC to afford (R)-N-(4-(3-((5-cyano-4-methoxypyrimidin-2-yl)amino)pyrrolidine-1-carbonyl)phenyl)acrylamide (55.6 mg, 45%) as white solid. ^{1}H NMR (400 MHz, DMSO-d_6): 2.01-2.22 (m, 2H), 3.29-3.34 (m, 3H), 3.46-3.84 (m, 4H), 4.57-4.68 (m, 1H), 5.78 (dd, J = 2.0, 10.0 Hz, 1H), 6.26-6.30 (m, 1H), 6.41-6.48 (m, 1H), 7.51-7.54 (m, 2H), 7.71-7.74 (m, 2H), 8.23-8.31 (m, 1H), 10.31 (s, 1H). [M+H] Calc'd for $C_{20}H_{20}N_6O_3$, 393.2; Found, 393.2.

Example 161: Synthesis of (N-(4-((3R)-3-((4-bromophenyl)amino)cyclopentanecarbonyl)-2-(2-(3,3-difluoropiperidin-1-yl)ethoxy)phenyl)acrylamide

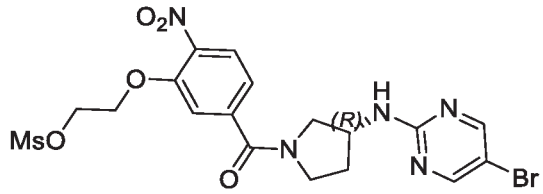


Step 1: (R)-(3-((5-bromopyrimidin-2-yl)amino)pyrrolidin-1-yl)(3-(2-hydroxyethoxy)-4-nitrophenyl)methanone



[00634] To a mixture of ethane-1,2-diol (3.60 mL, 64.7 mmol) in THF (30 mL) was added NaH (282 mg, 7.04 mmol, 60%) at ice-bath. The reaction mixture was stirred at for 20 min. Then (R)-(3-((5-bromopyrimidin-2-yl)amino)pyrrolidin-1-yl)(3-fluoro-4-nitrophenyl)methanone (2.0 g, 6.40 mmol) was added. The reaction mixture was stirred at RT overnight, The mixture was diluted with water (30 mL) and extracted with EtOAc (30 mL*3). The combined organic layer was washed with brine (30 mL), dried over Na_2SO_4, filtered and concentrated and purified by silica gel chromatography (DCM:MeOH = 20:1) to afford (R)-(3-((5-bromopyrimidin-2-yl)amino)pyrrolidin-1-yl)(3-(2-hydroxyethoxy)-4-nitrophenyl)methanone (1.3g, 44%) as a brown solid. [M+H] Calc'd for $C_{17}H_{18}BrN_5O_5$, 452.2; Found, 452.2

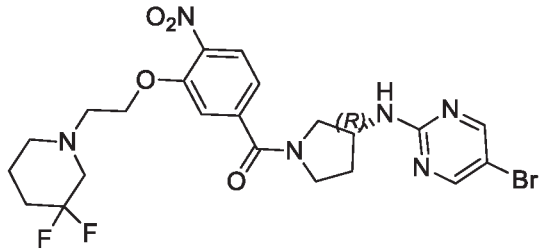
Step 2: (R)-2-(5-(3-((5-bromopyrimidin-2-yl)amino)pyrrolidine-1-carbonyl)-2-nitrophenoxy)ethyl methanesulfonate



[00635] To a solution of (R)-(3-((5-bromopyrimidin-2-yl)amino)pyrrolidin-1-yl)(3-(2-hydroxyethoxy)-4-nitrophenyl)methanone (600 mg, 1.32 mmol) in DCM (20 mL) was added TEA (201 mg, 1.99 mmol) in an ice-bath. Then a solution of methanesulfonyl chloride (167.1 mg, 1.46 mmol) in DCM (2 mL) was added dropwise at 0°C. The solution was stirred at 0°C for 2 hours. The solution was concentrated to afford (R)-2-(5-(3-((5-bromopyrimidin-2-yl)amino)pyrrolidine-1-carbonyl)-2-

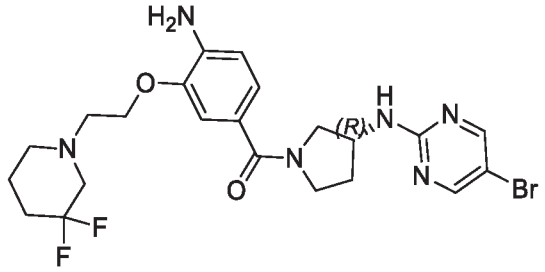
nitrophenoxy)ethyl methanesulfonate (650 mg, 92%) as a yellow solid which was used to the next step directly. [M+H] Calc'd for $C_{18}H_{20}BrN_5O_7S$,530.3; Found, 530.3

Step 3: (R)-(3-((5-bromopyrimidin-2-yl)amino)pyrrolidin-1-yl)(3-(2-(3,3-difluoropiperidin-1-yl)ethoxy)-4-nitrophenyl)methanone



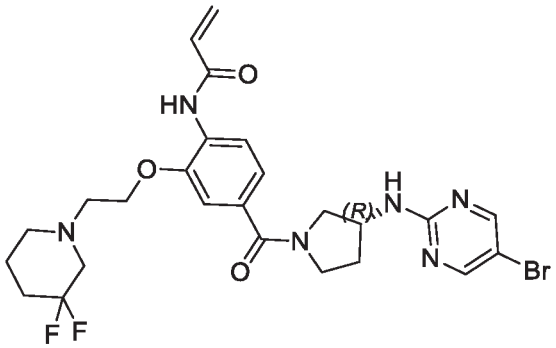
[00636] A mixture of (R)-2-(5-(3-((5-bromopyrimidin-2-yl)amino)pyrrolidine-1-carbonyl)-2-nitrophenoxy)ethyl methanesulfonate (650 mg, 1.22 mmol), 3,3-difluoropiperidine hydrochloride (347.6 mg, 2.20 mmol) and TEA (372 mg, 3.67 mmol) in DMF (20 mL) was stirred at 80°C for 16 h under N_2 balloon conditions. The reaction mixture was extracted with EtOAc (30 mL*3). The combined organic layer was washed with brine (30 mL), dried over Na_2SO_4, filtered and concentrated and purified by silica gel chromatography (DCM:MeOH = 20:1) to afford (R)-(3-((5-bromopyrimidin-2-yl)amino)pyrrolidin-1-yl)(3-(2-(3,3-difluoropiperidin-1-yl)ethoxy)-4-nitrophenyl)methanone (150 mg, 22%) as brown solid. [M+H] Calc'd for $C_{22}H_{25}BrF_2N_6O_4$, 555.3; Found, 555.3

Step 4: (R)-(4-amino-3-(2-(3,3-difluoropiperidin-1-yl)ethoxy)phenyl)(3-((5-bromopyrimidin-2-yl)amino)pyrrolidin-1-yl)methanone



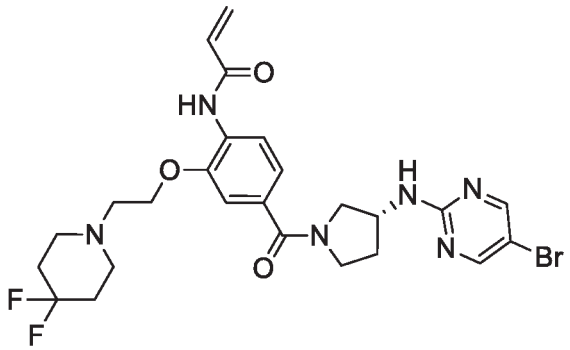
[00637] To a mixture of (R)-(3-((5-bromopyrimidin-2-yl)amino)pyrrolidin-1-yl)(3-(2-(3,3-difluoropiperidin-1-yl)ethoxy)-4-nitrophenyl)methanone (150 mg, 0.27 mmol) in MeOH/H_2O (20/5 mL) was added NH_4Cl (146 mg, 2.70 mmol) at RT. The reaction mixture was stirred at 70°C for 1h. Then added Zn (175 mg, 2.70 mmol) to reaction mixture and stirred at 70°C for 2h. The mixture was cooled, filtered and concentrated. The residue was purified by silica gel chromatography (DCM/MeOH = 20/1) to afford (R)-(4-amino-3-(2-(3,3-difluoropiperidin-1-yl)ethoxy)phenyl)(3-((5-bromopyrimidin-2-yl)amino)pyrrolidin-1-yl)methanone (100 mg, 70%) as a brown solid. [M+H] Calc'd for $C_{22}H_{27}BrF_2N_6O_2$, 525.3; Found, 525.3

Step 5: (R)-N-(4-(3-((5-bromopyrimidin-2-yl)amino)pyrrolidine-1-carbonyl)-2-(2-(3,3-difluoropiperidin-1-yl)ethoxy)phenyl)acrylamide



[00638] To a mixture of (R)-(4-amino-3-(2-(3,3-difluoropiperidin-1-yl)ethoxy)phenyl)(3-((5-bromopyrimidin-2-yl)amino)pyrrolidin-1-yl)methanone (100 mg, 0.19 mmol) in DCM (10 mL) was added DIEA (49.1 mg, 0.38 mmol) and Acryloyl chloride (17.2 mg, 0.19 mmol) at ice-bath. The reaction mixture was stirred at 0°C for 1h. The mixture was concentrated and purified by prep-HPLC to afford (R)-N-(4-(3-((5-bromopyrimidin-2-yl)amino)pyrrolidine-1-carbonyl)-2-(2-(3,3-difluoropiperidin-1-yl)ethoxy)phenyl)acrylamide (3.9 mg, 3.5%) as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6): 1.61-1.62 (m, 2H), 1.80-2.13 (m, 5H), 2.29-2.32 (m, 1H), 2.75-2.89 (m, 4H), 3.24-3.28 (m, 1H), 3.53-3.79 (m, 3H), 4.17-4.18 (m, 3H), 5.74-5.77 (d, J = 10.0 Hz, 1H), 6.24-6.26 (d, J = 10.0 Hz, 1H), 6.63-6.68 (m, 1H), 7.08-7.23 (m, 2H), 7.82 (s, 1H), 8.08-8.10 (m, 1H), 8.36-8.42 (m, 2H), 9.22-9.23 (m, 1H). [M+H] Calc'd for $C_{25}H_{29}BrF_2N_6O_3$, 579.4; Found, 579.4

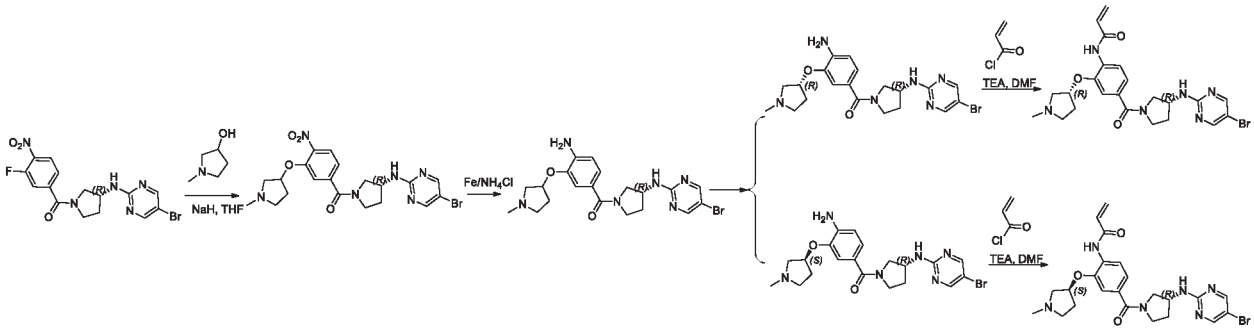
Example 162: Synthesis of (R)-N-(4-(3-((5-bromopyrimidin-2-yl)amino)pyrrolidine-1-carbonyl)-2-(2-(4,4-difluoropiperidin-1-yl)ethoxy)phenyl)acrylamide



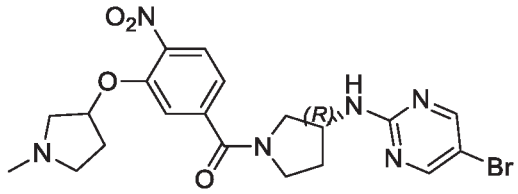
[00639] The title compound was prepared in 14.3% yield from {4-Amino-3-[2-(4,4-difluoro-piperidin-1-yl)-ethoxy]-phenyl}-[3-(5-bromo-pyrimidin-2-ylamino)-pyrrolidin-1-yl]-methanone using general procedure of (R)-N-(4-(3-((5-bromopyrimidin-2-yl)amino)pyrrolidine-1-carbonyl)-2-(2-(3,3-difluoropiperidin-1-yl)ethoxy)phenyl)acrylamide (55.1 mg, 14.3%) as brown solid. ^{1}H NMR (400 MHz, DMSO-d6): 1.88-1.93 (m, 5H), 2.14-2.41 (m, 1H), 2.56-2.59 (m,4H), 2.84-2.86 (m, 2H), 3.33-3.79 (m, 4H), 4.19-4.21 (m, 3H), 5.75-5.77 (d, J = 10.0 Hz, 1H), 6.23-6.27 (d, J = 10.0 Hz,

1H), 6.63-6.65 (m, 1H), 7.08-7.24 (m, 2H), 7.83 (s, 1H), 8.08-8.17 (m, 1H), 8.36-8.43(m, 2H), 9.28-9.29 (m, 1H). [M+H] Calc'd for $C_{25}H_{29}BrF_2N_6O_3$, 579.4; Found, 579.4.

Example 163 & 164: Synthesis of N-(4-((R)-3-((5-bromopyrimidin-2-yl)amino)pyrrolidine-1-carbonyl)-2-(((R)-1-methylpyrrolidin-3-yl)oxy)phenyl)acrylamide

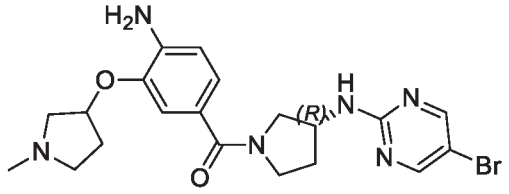


Step 1: ((R)-3-((5-bromopyrimidin-2-yl)amino)pyrrolidin-1-yl)(3-((1-methylpyrrolidin-3-yl)oxy)-4-nitrophenyl)methanone



[00640] To a mixture of 1-methylpyrrolidin-3-ol (247 mg, 2.44 mmol) in THF (10 mL) was added NaH (117 mg, 4.88 mmol, 60%) at 0°C and the reaction mixture was stirred at 0°C for 15 min. Then to the mixture was added (R)-(3-((5-bromopyrimidin-2-yl)amino)pyrrolidin-1-yl)(3-fluoro-4-nitrophenyl)methanone (1.0 g, 2.44 mmol) and the mixture was stirred at 0°C for 1h. The reaction was quenched with H_2O (10 mL) and concentrated. The residue was purified by silica gel chromatography (MeOH/EA = 3/7) to afford ((R)-3-((5-bromopyrimidin-2-yl)amino)pyrrolidin-1-yl)(3-((1-methylpyrrolidin-3-yl)oxy)-4-nitrophenyl)methanone (873 mg, 73%) as a brown solid. [M+H] Calc'd for $C_{20}H_{23}BrN_6O_4$, 491.1; Found, 491.1

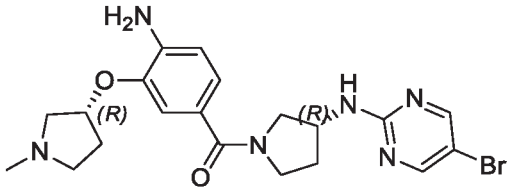
Step 2: (4-amino-3-((1-methylpyrrolidin-3-yl)oxy)phenyl)((R)-3-((5-bromopyrimidin-2-yl)amino)pyrrolidin-1-yl)methanone

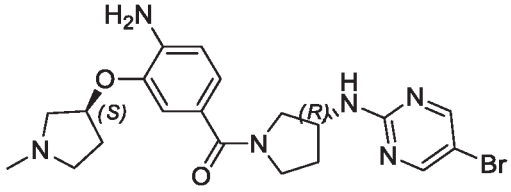


[00641] To a mixture of ((R)-3-((5-bromopyrimidin-2-yl)amino)pyrrolidin-1-yl)(3-((1-methylpyrrolidin-3-yl)oxy)-4-nitrophenyl)methanone (784 mg, 1.6 mmol) in EtOH/H_2O (10 mL/10 mL) was added

NH_4Cl (864 mg, 16.0 mmol) and Fe (896 mg, 16.0 mmol) at RT. The reaction mixture was stirred at 80°C for 5h. The mixture was cooled, filtered and concentrated. The residue was purified by silica gel chromatography (DCM/MeOH = 7/1) to afford a racemic mixture of (4-amino-3-((1-methylpyrrolidin-3-yl)oxy)phenyl)((R)-3-((5-bromopyrimidin-2-yl)amino)pyrrolidin-1-yl)methanone (566 mg, 77%) as a white solid. [M+H] Calc'd for $C_{20}H_{25}BrN_6O_2$, 461.1; Found, 461.1.

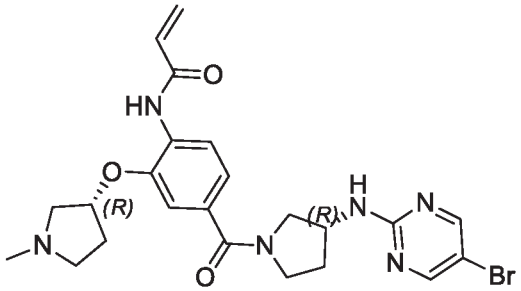
Step 3: (4-amino-3-(((R)-1-methylpyrrolidin-3-yl)oxy)phenyl)((R)-3-((5-bromopyrimidin-2-yl)amino)pyrrolidin-1-yl)methanone and (4-amino-3-(((S)-1-methylpyrrolidin-3-yl)oxy)phenyl)((R)-3-((5-bromopyrimidin-2-yl)amino)pyrrolidin-1-yl)methanone





[00642] A racemic mixture of (4-amino-3-((1-methylpyrrolidin-3-yl)oxy)phenyl)((R)-3-((5-bromopyrimidin-2-yl)amino)pyrrolidin-1-yl)methanone (566 mg) was purified by chiral sepration (IC: Hex:EtOH/DEA = 40:60:0.3, 12mL/min, 254 nm) to give (4-amino-3-(((R)-1-methylpyrrolidin-3-yl)oxy)phenyl)((R)-3-((5-bromopyrimidin-2-yl)amino)pyrrolidin-1-yl)methanone (208 mg, 12.05min) and (4-amino-3-(((S)-1-methylpyrrolidin-3-yl)oxy)phenyl)((R)-3-((5-bromopyrimidin-2-yl)amino)pyrrolidin-1-yl)methanone (116 mg, 14.19 min) as a white solid.

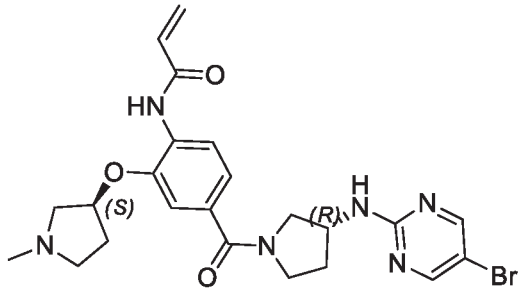
Step 4: N-(4-((R)-3-((5-bromopyrimidin-2-yl)amino)pyrrolidine-1-carbonyl)-2-(((R)-1-methylpyrrolidin-3-yl)oxy)phenyl)acrylamide



[00643] To a mixture of (4-amino-3-(((R)-1-methylpyrrolidin-3-yl)oxy)phenyl)((R)-3-((5-bromopyrimidin-2-yl)amino)pyrrolidin-1-yl)methanone (208 mg, 0.45 mmol) in DCM/DMF (5 mL/2 mL) was added DIEA (116 mg, 0.90 mmol) and Acryloyl chloride (36 mg, 0.45 mmol) in an ice-bath. It was stirred at 0°C for 1h. The mixture was concentrated and purified by prep-HPLC to afford N-(4-((R)-3-((5-bromopyrimidin-2-yl)amino)pyrrolidine-1-carbonyl)-2-(((R)-1-methylpyrrolidin-3-yl)oxy)phenyl)acrylamide (37.8 mg, 16%) as white solid. ^1H NMR (400 MHz, DMSO-d_6): 1.89-

2.19 (m, 4H), 2.24-2.34 (m, 3.5H), 2.63-2.78 (m, 3.5H), 3.51-3.79 (m, 4H), 4.22-4.41 (m, 1H), 4.87-4.92 (m, 1H), 5.77 (d, J = 10.0 Hz, 1H), 6.23-6.28 (m, 1H), 6.65-6.72 (m, 1H), 7.05-7.09 (m, 2H), 7.82 (s, 1H), 8.12-8.17 (m, 1H), 8.36 (s, 1H), 8.43 (s, 1H), 9.34-9.36 (m, 1H). [M+H] Calc'd for $C_{23}H_{27}BrN_6O_3$, 515.1; Found, 515.1.

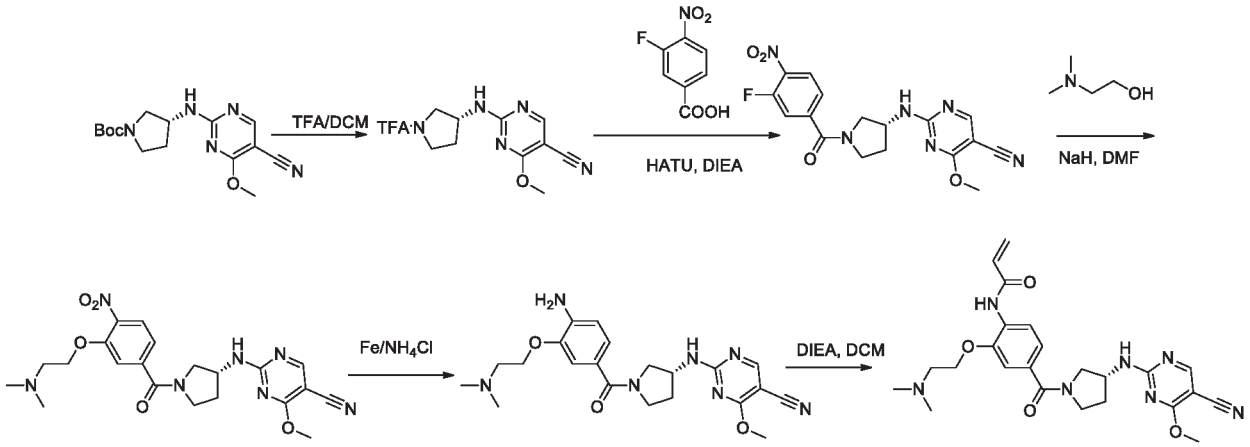
Step 5: N-(4-((R)-3-((5-bromopyrimidin-2-yl)amino)pyrrolidine-1-carbonyl)-2-(((S)-1-methylpyrrolidin-3-yl)oxy)phenyl)acrylamide



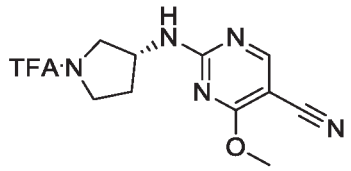
[00644] To a mixture of (4-amino-3-(((S)-1-methylpyrrolidin-3-yl)oxy)phenyl)((R)-3-((5-bromopyrimidin-2-yl)amino)pyrrolidin-1-yl)methanone (190 mg, 0.41 mmol) in DCM/DMF (5 mL/2 mL) was added DIEA (106 mg, 0.82 mmol) and Acryloyl chloride (33 mg, 0.41 mmol) in an ice-bath and the reaction mixture was stirred at 0°C for 1h. The mixture was concentrated and purified by prep-HPLC to afford N-(4-((R)-3-((5-bromopyrimidin-2-yl)amino)pyrrolidine-1-carbonyl)-2-(((S)-1-methylpyrrolidin-3-yl)oxy)phenyl)acrylamide (27.4 mg, 13%) as white solid.

^{1}H NMR (400 MHz, DMSO-d_6): 1.85-1.94 (m, 2H), 2.10-2.32 (m, 5H), 2.59-2.75 (m, 4H), 3.49-3.78 (m, 4H), 4.21-4.41(m, 1H), 4.85-4.92 (m, 1H), 5.77 (d, J = 10.0 Hz, 1H), 6.65-6.72 (m, 1H), 7.03-7.13 (m, 1H), 7.82 (s, 1H), 8.12-8.17 (m, 1H), 8.36 (s, 1H), 8.43 (s, 1H), 9.32-9.33 (m, 1H). [M+H] Calc'd for $C_{23}H_{27}BrN_6O_3$, 515.1; Found, 515.1

Example 165: Synthesis of (R)-N-(4-(3-((5-cyano-4-methoxypyrimidin-2-yl)amino)pyrrolidine-1-carbonyl)-2-(2-(dimethylamino)ethoxy)phenyl)acrylamide

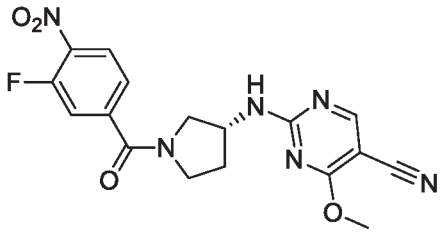


Step 1: (R)-4-methoxy-2-(pyrrolidin-3-ylamino)pyrimidine-5-carbonitrile hydrochloride



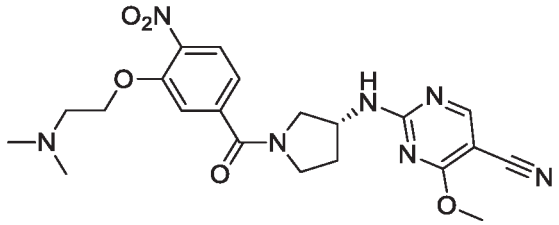
[00645] The title compound was prepared in 100% yield from (R)-tert-butyl 3-((5-cyano-4-methoxypyrimidin-2-yl)amino)pyrrolidine-1-carboxylate using general procedure of (R)-4-methoxy-2-(pyrrolidin-3-ylamino)pyrimidine-5-carbonitrile 2,2,2-trifluoroacetate. [M+H] Calc'd for $C_{12}H_{12}F_3N_5O_2$ 316.1; Found, 316.3

Step 2: (R)-2-((1-(3-fluoro-4-nitrobenzoyl)pyrrolidin-3-yl)amino)-4-methoxypyrimidine-5-carbonitrile



[00646] To a mixture of (R)-4-methoxy-2-(pyrrolidin-3-ylamino)pyrimidine-5-carbonitrile 2,2,2-trifluoroacetate (214 mg, 0.98 mmol), DIEA (379 mg, 2.94 mmol) and HATU (447 mg, 1.18 mmol) in DCM (5 mL) was added 3-fluoro-4-nitrobenzoic acid (181 mg, 0.98 mmol) in an ice-bath. After stirring at RT for 1h, the mixture was concentrated and purified by flash (DCM/MeOH=10/1) to afford (R)-2-((1-(3-fluoro-4-nitrobenzoyl)pyrrolidin-3-yl)amino)-4-methoxypyrimidine-5-carbonitrile (590 mg, 100%) as yellow oil. [M+H] Calc'd for $C_{17}H_{15}FN_6O_4$ 387.1; Found, 387.3

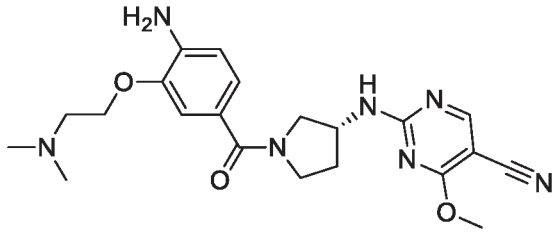
Step 3: (R)-2-((1-(3-(2-(dimethylamino)ethoxy)-4-nitrobenzoyl)pyrrolidin-3-yl)amino)-4-methoxypyrimidine-5-carbonitrile



[00647] To a mixture of 2-(dimethylamino)ethanol (133 mg, 1.5 mmol) in DMF (2 mL) was added NaH (60 mg, 1.5 mmol, 60%) at 0°C and the reaction mixture was stirred at 0°C for 15 min. To the mixture was added (R)-2-((1-(3-fluoro-4-nitrobenzoyl)pyrrolidin-3-yl)amino)-4-methoxypyrimidine-5-carbonitrile (590 mg, 1.5 mmol) and the mixture was stirred at RT for overnight. The reaction was quenched with H_2O (10 mL) and concentrated. The residue was purified by silica gel chromatography (DCM/MeOH = 10/1) to afford (R)-2-((1-(3-(2-(dimethylamino)ethoxy)-4-

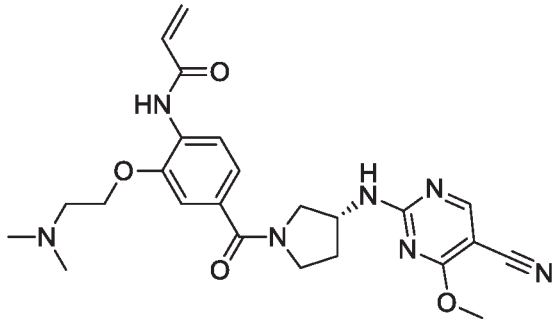
nitrobenzoyl)pyrrolidin-3-yl)amino)-4-methoxypyrimidine-5-carbonitrile (332 mg, 84%) as yellow oil. [M+H] Calc'd for $C_{21}H_{25}N_7O_5$, 456.2; Found, 456.1

Step 4: (R)-2-((1-(4-amino-3-(2-(dimethylamino)ethoxy)benzoyl)pyrrolidin-3-yl)amino)-4-methoxypyrimidine-5-carbonitrile



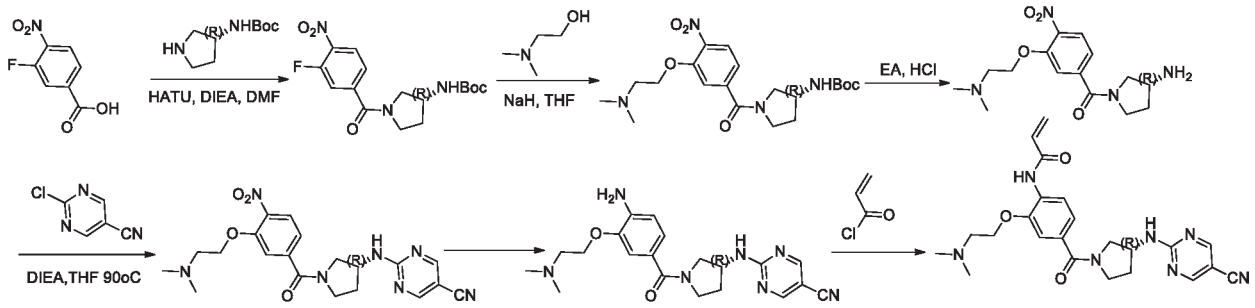
[00648] To a mixture of (R)-2-((1-(3-(2-(dimethylamino)ethoxy)-4-nitrobenzoyl)pyrrolidin-3-yl)amino)-4-methoxypyrimidine-5-carbonitrile (330 mg, 0.73 mmol) in EtOH/H_2O (10 mL/10 mL) was added NH_4Cl (394 mg, 7.3 mmol) and Fe (409 mg, 7.3 mmol) at RT. The reaction mixture was stirred at 80°C for 5h. The mixture was cooled, filtered and concentrated. The residue was purified by flash (DCM/MeOH = 10/1) to afford (R)-2-((1-(4-amino-3-(2-(dimethylamino)ethoxy)benzoyl)pyrrolidin-3-yl)amino)-4-methoxypyrimidine-5-carbonitrile (123 mg, 40%) as a brown solid. [M+H] Calc'd for $C_{21}H_{27}N_7O_3$, 426.2; Found, 426.1

Step 5: (R)-N-(4-(3-((5-cyano-4-methoxypyrimidin-2-yl)amino)pyrrolidine-1-carbonyl)-2-(2-(dimethylamino)ethoxy)phenyl)acrylamide

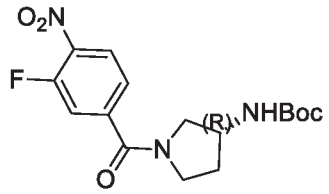


[00649] To a mixture of (R)-2-((1-(4-amino-3-(2-(dimethylamino)ethoxy)benzoyl)pyrrolidin-3-yl)amino)-4-methoxypyrimidine-5-carbonitrile (123 mg, 0.29 mmol) in DCM/DMF (5 mL/2 mL) was added DIEA (75 mg, 0.58 mmol) and Acryloyl chloride (23 mg, 0.29 mmol) in an ice-bath and the reaction mixture was stirred at 0°C for 1h. The mixture was concentrated and purified by prep-HPLC to afford (R)-N-(4-(3-((5-cyano-4-methoxypyrimidin-2-yl)amino)pyrrolidine-1-carbonyl)-2-(2-(dimethylamino)ethoxy)phenyl)acrylamide (29.6 mg, 21%) as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6): 1.92-2.03 (m, 1H), 2.13-2.24 (m, 7H), 2.61-2.62 (m, 2H), 3.39-3.84 (m, 4H), 3.88-4.01 (m, 3H), 4.14-4.17 (m, 2H), 4.38-4.56 (m, 1H), 5.78 (d, J = 11.2 Hz, 1H), 6.24-6.28 (m, 1H), 6.52-6.59 (m, 1H), 7.14-7.27 (m, 2H), 8.13-8.18 (m, 1H) 8.47-8.65 (m, 2H), 9.67-9.69 (m, 1H). [M+H] Calc'd for $C_{24}H_{29}N_7O_4$, 480.2; Found, 480.2

Example 166: (R)-N-(4-(3-((5-cyanopyrimidin-2-yl)amino)pyrrolidine-1-carbonyl)-2-(2-(dimethylamino)ethoxy)phenyl)acrylamide

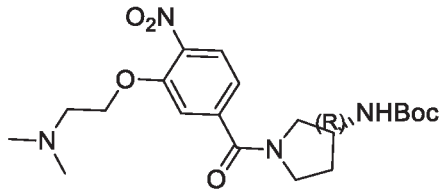


Step 1: (R)-tert-butyl (1-(3-fluoro-4-nitrobenzoyl)pyrrolidin-3-yl)carbamate



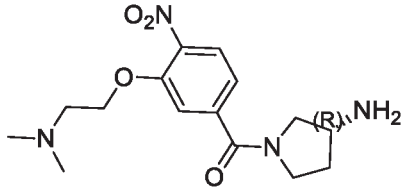
[00650] To a solution of 3-fluoro-4-nitrobenzoic acid (3.0 g, 16.2 mmol) and (R)-tert-butyl pyrrolidin-3-ylcarbamate (3.1 g, 14.6 mmol) in DMF (60 mL) was added HATU (6.7 g,17.8 mmol) and DIEA (6.2 g, 48.6 mmol) at ice-bath. The mixture was stirred at RT for 2h. The mixture was diluted with water (200 mL) and extracted with EA (100 mL*2). The combined organic layer was washed with brine (100 mL), dried over Na_2SO_4, filtered and ether evaporated. The residue was purified by coclumn chromatography to afford 5 g of product as a yellow solid. [M+H] Calc'd for $C_{16}H_{20}FN_3O_5$, 354.1; Found, 354.1

Step 2: (R)-tert-butyl (1-(3-(2-(dimethylamino)ethoxy)-4-nitrobenzoyl)pyrrolidin-3-yl)carbamate



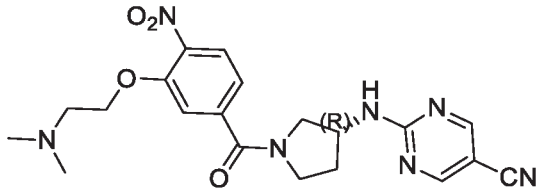
[00651] To a solution of 2-(dimethylamino)ethanol (1.5 g，17.0 mmol) in THF (80 mL) was added NaH (680 mg, 17.0 mmol, 60%) in an ice-bath. The reaction mixture was then stirred at RT for 0.5 h. Then (R)-tert-butyl (1-(3-fluoro-4-nitrobenzoyl)pyrrolidin-3-yl)carbamate (5.0 g, 14.1 mmol) was added and the mixture was stirred at RT for 2h. The mixture was concentrated in-vacuo and to the residue was added water and extracted with EA. The combined organic layer was washed with brine (100 mL), dried over Na_2SO_4, filtered and ether evaporated. The residue was purified by column chromatography to afford 3.6 g of product as a yellow solid. [M+H] Calc'd for $C_{20}H_{30}N_4O_6$, 423.2; Found, 423.2

Step 3: (R)-(3-aminopyrrolidin-1-yl)(3-(2-(dimethylamino)ethoxy)-4-nitrophenyl)methanone



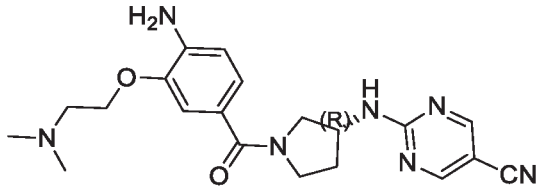
[00652] To a solution of (R)-tert-butyl (1-(3-(2-(dimethylamino)ethoxy)-4-nitrobenzoyl)pyrrolidin-3-yl)carbamate (3.6 g, 8.5 mmol) in EA (50 mL) was bubbled HCl (gas) at -50°C and the reaction mixture was stirred at RT for 3h. The mixture was concentrated to afford 2.4 g crude product as a yellow solid. [M+H] Calc'd for $C_{20}H_{30}N_4O_6$, 323.2; Found, 323.2

Step 4: (R)-2-((1-(3-(2-(dimethylamino)ethoxy)-4-nitrobenzoyl)pyrrolidin-3-yl)amino)pyrimidine-5-carbonitrile



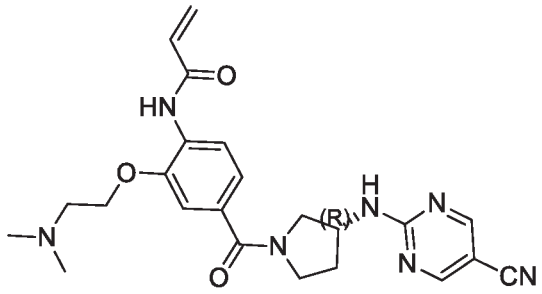
[00653] To a solution of (R)-(3-aminopyrrolidin-1-yl)(3-(2-(dimethylamino)ethoxy)-4-nitrophenyl)methanone (1.0 g, 3.1 mmol) and DIEA (1.2 g, 9.3 mmol) in DMA (15 mL) was added a solution of 2-chloropyrimidine-5-carbonitrile (640 mg, 2.8 mmol) in an ice-bath and the reaction mixture was warmed to RT and stirred for 2h. Then to the mixture was added water (20 mL) which was used directly in the next step. [M+H] Calc'd for $C_{20}H_{23}N_7O_4$, 426.1; Found, 426.1

Step 5: (R)-2-((1-(4-amino-3-(2-(dimethylamino)ethoxy)benzoyl)pyrrolidin-3-yl)amino)pyrimidine-5-carbonitrile



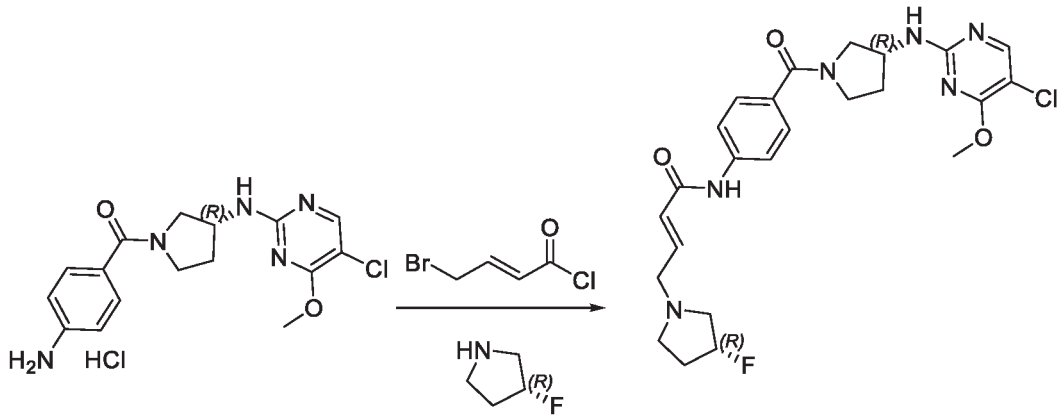
[00654] To a solution of (R)-2-((1-(3-(2-(dimethylamino)ethoxy)-4-nitrobenzoyl)pyrrolidin-3-yl)amino)pyrimidine-5-carbonitrile (1.0 g, 2.3 mmol) in ethanol (60 mL) and water (20 mL) was added NH_4Cl (1.2 g, 23.5 mmol) and Fe (1.3 g, 23.5 mmol) at RT.The reaction mixture was then stirred at 80°C for 2h. The mixture was filtered and concentrated and the residue was purified by column chromatography to afford 700 mg crude product as a yellow solid. [M+H] Calc'd for $C_{20}H_{30}N_4O_6$, 396.2; Found, 396.2

Step 6: (R)-N-(4-(3-((5-cyanopyrimidin-2-yl)amino)pyrrolidine-1-carbonyl)-2-(2-(dimethylamino)ethoxy)phenyl)acrylamide



[00655] To a solution of (R)-2-((1-(4-amino-3-(2-(dimethylamino)ethoxy)benzoyl)pyrrolidin-3-yl)amino)pyrimidine-5-carbonitrile (700 mg, 1.77 mmol) and DIEA (687 mg, 5.31 mmol) in DCM (30 mL) and DMF (3 mL) was added acryloyl chloride (238 mg, 2.65 mmol) in an ice-bath. The reaction mixture was then warmed to RT and stirred for 2h. The reaction mixture was concentrated and the residue was purified by prep-HPLC to afford (R)-N-(4-(3-((5-cyanopyrimidin-2-yl)amino)pyrrolidine-1-carbonyl)-2-(2-(dimethylamino)ethoxy)phenyl)acrylamide (152.5 mg, 19%) as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6): 1.89-2.03 (m, 1H), 2.03-2.21 (m, 1H), 2,22-2,24 (d, J = 6.4 Hz, 6H), 2.60-2.62 (m, 2H), 3.31-3.65 (m, 4H), 4.13-4.17 (m, 2H), 4.39 (s, 0.5H), 4.52 (s, 0.5H), 5.76-5.79 (d, J = 10 Hz, 1H), 6.24-6.28 (d, J = 16.8 Hz, 1H), 6.52-6.59 (m, 1H), 7.14-7.15 (t, J = 14.0 Hz, 1H), 7.23-7.27 (d, J = 14.0 Hz, 1H), 8.14-8.17 (t, J = 14.0 Hz, 1H) ，8.64-8.78 (m, 3H), 9.65-9.68 (d, J = 12.4 Hz, 1H). [M+H] Calc'd for $C_{23}H_{27}N_7O_3$, 450.2; Found, 450.2

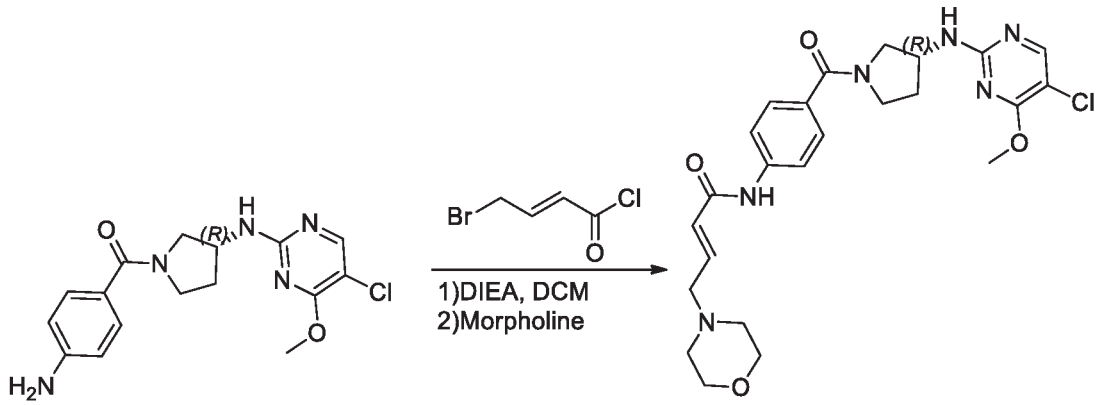
Example 167: Synthesis of (E)-N-(4-((R)-3-((5-chloro-4-methoxypyrimidin-2-yl)amino)pyrrolidine-1-carbonyl)phenyl)-4-((R)-3-fluoropyrrolidin-1-yl)but-2-enamide



[00656] To a solution of (R)-(4-aminophenyl)(3-((5-chloro-4-methoxypyrimidin-2-yl)amino)pyrrolidin-1-yl)methanone hydrochloride (174 mg, 0.5 mmol) and DIEA (194 mg, 1.5 mmol) in DCM (10 mL) was added a solution of (E)-4-bromobut-2-enoyl chloride (184 mg, 1.0 mmol) in DCM (5 mL) in an ice-bath. The mixture was stirred in the ice-bath for 1h and then (R)-3-fluoropyrrolidine (53 mg, 0.6 mmol) was added to the mixture and the mixture was stirred at RT for 5h. The mixture was concentrated and purified by prep-HPLC to afford (E)-N-(4-((R)-3-((5-chloro-4-methoxypyrimidin-2-yl)amino)pyrrolidine-1-carbonyl)phenyl)-4-((R)-3-fluoropyrrolidin-1-yl)but-2-enamide (23 mg,

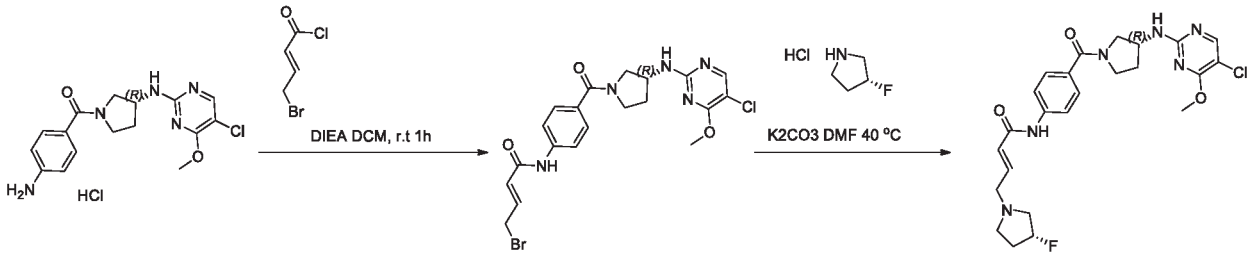
9%) as a yellow solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.89-1.90 (m, 2H), 1.97-2.16 (m, 2H), 2.33-2.40 (m, 2H), 2.58-2.68 (m, 2H), 2.84-2.87 (m, 2H), 3.28-3.64 (m, 4H), 3.77-3.93 (m, 3H), 4.26-4.40 (m, 1H), 5.14-5.28 (m, 1H), 6.28-6.32 (m, 1H), 6.77-6.81 (m, 1H), 7.47-7.52 (m, 2H), 7.67-7.72 (m, 3H), 8.07-8.14 (m, 1H), 10.24 (s, 1H). [M+H] Calc'd for $C_{24}H_{28}ClFN_6O_3$, 503.1; Found, 503.1

Example 168: Synthesis of (R,E)-N-(4-(3-((5-chloro-4-methoxypyrimidin-2-yl)amino)pyrrolidine-1-carbonyl)phenyl)-4-morpholinobut-2-enamide

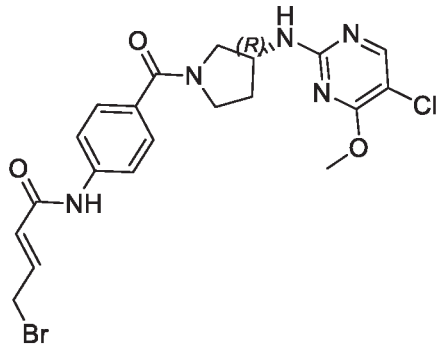


To a solution of (R)-(4-aminophenyl)(3-((5-chloro-4-methoxypyrimidin-2-yl)amino)pyrrolidin-1-yl)methanone (400 mg, 1.15 mmol) and DIEA(593 mg, 4.6 mmol) in DCM (10 mL) was added (E)-4-bromobut-2-enoyl chloride (423 mg, 2.3 mmol) in an ice-bath. The mixture was stirred at RT for 1h. Morpholine (200 mg, 2.3 mmol) was added to the mixture and stirred at RT for overnight. The mixture was concentrated and purified by prep-HPLC to afford (R,E)-N-(4-(3-((5-chloro-4-methoxypyrimidin-2-yl)amino)pyrrolidine-1-carbonyl)phenyl)-4-morpholinobut-2-enamide (66.5 mg, 12%) as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6): 1.90-2.15 (m, 2H), 2.39 (s, 4H), 3.12 (d, J = 4.4 Hz, 2H), 3.38-3.64 (m, 7H), 3.78-3.94 (m, 4H), 4.25 (s, 0.5H), 4.42 (s, 0.5H), 6.27 (s, 0.5H), 6.31 (s, 0.5H), 6.73-6.77 (m, 1H), 7.50 (t, J = 8.4 Hz, 2H), 7.70 (t, J = 8.4 Hz, 3H), 8.07 (s, 0.5H), 8.15 (s, 0.5H), 10.23 (s, 1H). [M+H] Calc'd for $C_{24}H_{29}ClN_6O_4$, 501.2 Found, 501.2

Example 169: (R)-N-(4-(3-((5-bromopyrimidin-2-yl)amino)pyrrolidine-1-carbonyl)-2-(4-(dimethylamino)piperidin-1-yl)phenyl)acrylamide

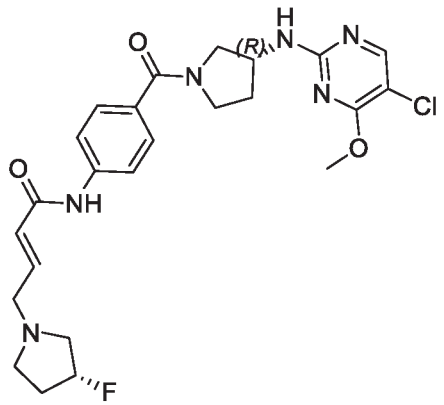


Step 1:(R,E)-4-bromo-N-(4-(3-((5-chloro-4-methoxypyrimidin-2-yl)amino)pyrrolidine-1-carbonyl)phenyl)but-2-enamide



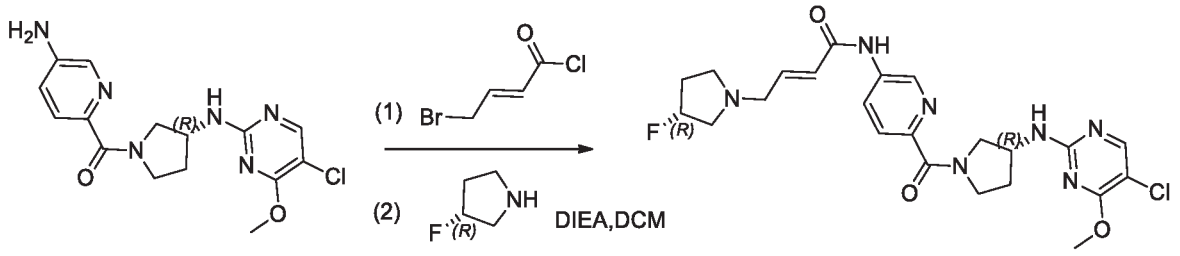
[00657] To a solution of (R)-(4-aminophenyl)(3-((5-chloro-4-methoxypyrimidin-2-yl)amino)pyrrolidin-1-yl)methanone (2.0 g, 5.8 mmol) and DIEA (3.7 g, 28.8 mmol) in DCM (50 mL) was added (E)-4-bromobut-2-enoyl chloride (2.1 g, 11.5 mmol) at ice-bath. The mixture was stirred at RT for 2h. The mixture was concentrated and columned to afford 800 mg crude product as a yellow solid. [M+H] Calc'd for $C_{20}H_{21}BrClN_5O_3$: 496.1 Found: 496.1

Step 2: (E)-N-(4-((R)-3-((5-chloro-4-methoxypyrimidin-2-yl)amino)pyrrolidine-1-carbonyl)phenyl)-4-((S)-3-fluoropyrrolidin-1-yl)but-2-enamide



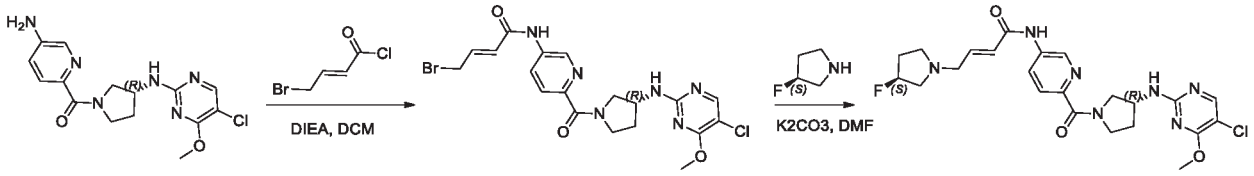
[00658] To a solution of (R,E)-4-bromo-N-(4-(3-((5-chloro-4-methoxypyrimidin-2-yl)amino)pyrrolidine-1-carbonyl)phenyl)but-2-enamide (200 mg, 0.4 mmol) and (S)-3-fluoropyrrolidine hydrochloride (71 mg, 0.8 mmol) in DMF (3 mL) was added K_2CO_3 (165 mg,1.2 mmol) at RT. The reaction mixture was stirred at 50°C for 2h. The reaction mixture was cooled, filtered and concentrated. The residue was purified by prep-HPLC to afford (E)-N-(4-((R)-3-((5-chloro-4-methoxypyrimidin-2-yl)amino)pyrrolidine-1-carbonyl)phenyl)-4-((S)-3-fluoropyrrolidin-1-yl)but-2-enamide (12.7 mg, 6%) as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6): 1.87-2.15 (m, 4H), 2.33-2.34 (m, 1H), 2.83-2.87 (m, 2H), 3.27-3.78 (m, 6H), 3.85 (s, 1.5H), 3.94 (s, 1.5H), 4.27 (s, 0.5H), 4.41 (s, 0.5H), 5.14-5.28 (m, 1H), 6.28 (s, 0.5H), 6.32 (s, 0.5H), 6.77-6.81 (m, 1H), 7.47-7.52 (t, J = 10.8 Hz, 2H), 7.67-7.71 (m, 3H), 8.07 (s, 0.5H), 8.14 (s, 0.5H), 10.22 (s, 1H). [M+H] Calc'd for $C_{24}H_{28}ClFN_6O_3$, 503.1 Found, 503.1

Example 170: Synthesis of (E)-N-(6-((R)-3-((5-chloro-4-methoxypyrimidin-2-yl)amino)pyrrolidine-1-carbonyl)pyridin-3-yl)-4-((R)-3-fluoropyrrolidin-1-yl)but-2-enamide

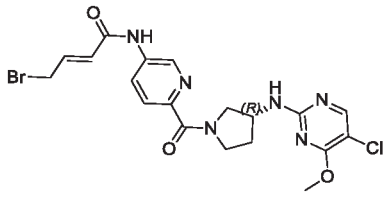


[00659] To a solution of (R)-(5-aminopyridin-2-yl)(3-((5-chloro-4-methoxypyrimidin-2-yl)amino)pyrrolidin-1-yl)methanone (200 mg, 0.57 mmol) and DIEA (220 mg, 1.71 mmol) in DCM (20 mL) was added (E)-4-bromobut-2-enoyl chloride (184 mg, 1.00 mmol) in DCM (5 mL) at ice-bath, after 1 h, (R)-3-fluoropyrrolidine (101 mg, 1.14 mmol) was added to the mixture and stirred at RT for 5 h. The mixture was concentrated *in vacuo* and purified by *prep*-HPLC to afford (E)-N-(6-((R)-3-((5-chloro-4-methoxypyrimidin-2-yl)amino)pyrrolidine-1-carbonyl)pyridin-3-yl)-4-((R)-3-fluoropyrrolidin-1-yl)but-2-enamide (39.4 mg, 14%) as a white solid. ^{1}H NMR (400 MHz, DMSO- d_6): δ 1.93-1.97 (m, 2H), 2.11-2.17 (m, 2H), 2.32-2.37 (m, 2H), 2.58-2.66 (m, 2H), 2.82-2.88 (m, 2H), 3.32-3.81 (m, 4H), 3.89-3.93 (m, 3H), 4.34-4.36 (m, 1H), 5.13-5.30 (m, 1H), 6.30-6.34 (m, 1H), 6.82-6.86 (m, 1H), 7.69-7.79 (m, 2H), 8.09-8.21 (m, 2H), 8.78-8.82 (m, 1H), 10.49-10.50 (m, 1H). [M+H] Calc'd for $C_{23}H_{27}ClFN_7O_3$, 504.2; Found, 504.2

Example 171: Synthesis of (E)-N-(6-((R)-3-((5-chloro-4-methoxypyrimidin-2-yl)amino)pyrrolidine-1-carbonyl)pyridin-3-yl)-4-((S)-3-fluoropyrrolidin-1-yl)but-2-enamide



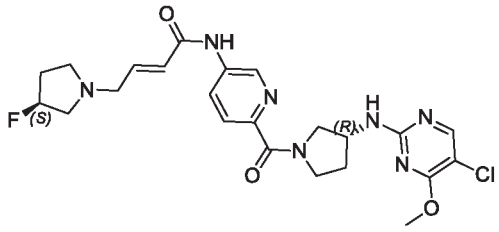
Step 1:(R,E)-4-bromo-N-(6-(3-((5-chloro-4-methoxypyrimidin-2-yl)amino)pyrrolidine-1-carbonyl)pyridin-3-yl)but-2-enamide



[00660] To a solution of (R)-(5-aminopyridin-2-yl)(3-((5-chloro-4-methoxypyrimidin-2-yl)amino)pyrrolidin-1-yl)methanone (500 mg, 1.40 mmol) and DIEA (722 mg, 1.71 mmol) in DCM (20 mL) was added (E)-4-bromobut-2-enoyl chloride (528 mg, 2.80 mmol) in DCM (10 mL) in an ice-bath. The reaction mixture was fitered and concentrated *in vacuo*. The residue was purified by silica gel chromatography to afford (R,E)-4-bromo-N-(6-(3-((5-chloro-4-

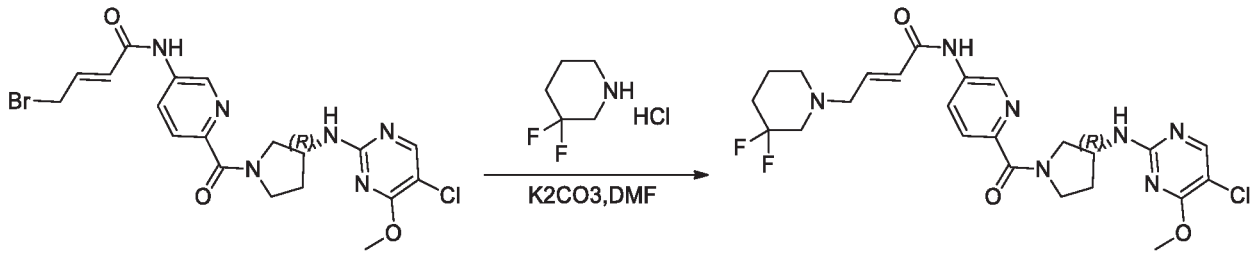
methoxypyrimidin-2-yl)amino)pyrrolidine-1-carbonyl)pyridin-3-yl)but-2-enamide (270 mg, 20%) as yellow solid. [M+H] Calc'd for $C_{19}H_{20}BrClN_6O_3$, 495.0; Found, 495.0

Step 2: Synthesis of (E)-N-(6-((R)-3-((5-chloro-4-methoxypyrimidin-2-yl)amino)pyrrolidine-1-carbonyl)pyridin-3-yl)-4-((S)-3-fluoropyrrolidin-1-yl)but-2-enamide



[00661] A solution of (R,E)-4-bromo-N-(6-(3-((5-chloro-4-methoxypyrimidin-2-yl)amino)pyrrolidine-1-carbonyl)pyridin-3-yl)but-2-enamide (100 mg, 0.2 mmol), (R)-3-fluoropyrrolidine (51 mg, 0.4 mmol) and K_2CO_3 (110 mg, 0.8 mmol) in DMF (10 mL) was stirred at RT for 16h. The mixture was concentrated *in vacuo*. The residue was purified by *prep*-HPLC to afford (E)-N-(6-((R)-3-((5-chloro-4-methoxypyrimidin-2-yl)amino)pyrrolidine-1-carbonyl)pyridin-3-yl)-4-((S)-3-fluoropyrrolidin-1-yl)but-2-enamide (23.2 mg, 23%) as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.93-1.97 (m, 2H), 2.12-2.17 (m, 2H), 2.34-2.36 (m, 2H), 2.57-2.69 (m, 2H), 2.82-2.88 (m, 2H), 3.53-3.69 (m, 4H), 3.80 -3.93 (m, 3H), 4.34-4.37 (m, 1H), 5.14-5.28 (m, 1H), 6.29-6.34 (m, 1H), 6.81-6.86 (m, 1H), 7.66-7.78 (m, 2H), 8.09-8.21 (m, 2H), 8.78-8.82 (m, 1H), 10.47-10.50 (m, 1H). [M+H] Calc'd for $C_{23}H_{27}ClFN_7O_3$, 504.2; Found, 504.2.

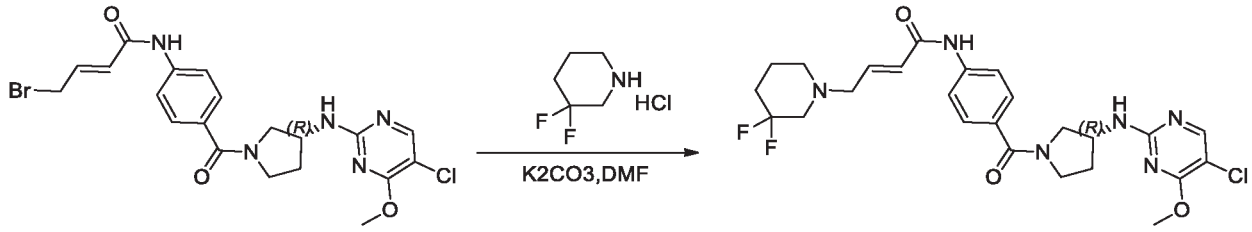
Example 172: Synthesis of (R,E)-N-(6-(3-((5-chloro-4-methoxypyrimidin-2-yl)amino)pyrrolidine-1-carbonyl)pyridin-3-yl)-4-(3,3-difluoropiperidin-1-yl)but-2-enamide



[00662] To a mixture of (R,E)-4-bromo-N-(6-(3-((5-chloro-4-methoxypyrimidin-2-yl)amino)pyrrolidine-1-carbonyl)pyridin-3-yl)but-2-enamide (70 mg, 0.2 mmol) and 3,3-difluoropiperidine (45 mg, 0.3 mmol) in DMF (10 mL) was added K_2CO_3 (97mg, 0.6 mmol) at 0°C. The reaction mixture was stirred at 25°C for 5h. The reaction was quenched with H_2O (10 mL) and extracted with EA (50 mL x 3). The combined organic layer was concentrated *in vacuo* and purified by *prep*-HPLC (NH_4CO_3 20%~50%) to afford (R,E)-N-(6-(3-((5-chloro-4-methoxypyrimidin-2-yl)amino)pyrrolidine-1-carbonyl)pyridin-3-yl)-4-(3,3-difluoropiperidin-1-yl)but-2-enamide (11mg, 15%) as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6): 1.70-1.75 (m, 2H), 1.87-2.17 (m, 4H), 2.46-2.52 (m, 2H), 2.52-2.75 (m, 2H), 3.26-3.28 (d, J = 8.0 Hz, 2H), 3.54-3.83 (m, 4H), 3.90-3.96 (m, 3H), 4.35-4.39 (m,

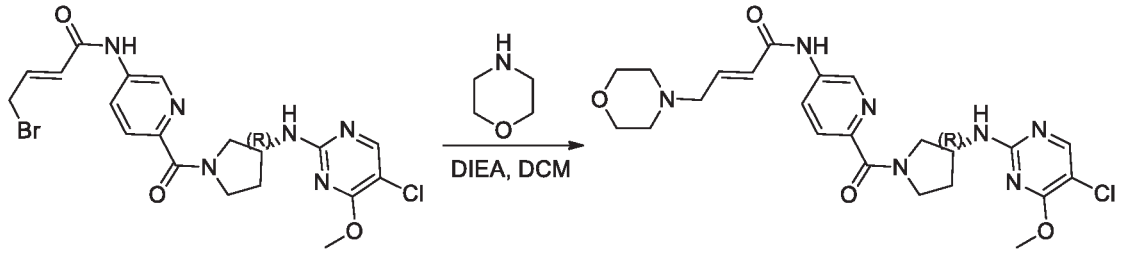
1H), 6.30-6.35 (m, 1H), 6.79-6.84 (m, 1H), 7.79-7.82 (m, 2H), 8.12-8.24 (m, 2H), 8.81-8.85 (m, 1H), 10.52-10.54 (m, 1H). [M+H] Calc'd for $C_{24}H_{28}ClF_2N_7O_3$, 536.1; Found, 536.2.

Example 173: (R,E)-N-(4-(3-((5-chloro-4-methoxypyrimidin-2-yl)amino)pyrrolidine-1-carbonyl)phenyl)-4-(3,3-difluoropiperidin-1-yl)but-2-enamide



[00663] To a mixture of (R)-(4-aminophenyl)(3-((5-chloro-4-methoxypyrimidin-2-yl)amino)pyrrolidin-1-yl)methanone (150 mg, 0.3 mmol) and 3,3-difluoropiperidine (45 mg, 0.3 mmol) in DMF (10 mL) was added K_2CO_3 (207 mg, 1.5 mmol) at 0°C. The reaction mixture was then stirred at 40°C for 13h. The reaction was cooled, quenched with H_2O (10 mL) and extracted with EA (50 mL*3). The combind organic layer was concentrated *in vacuo* and purified by *prep*-HPLC (HCOOH 10%~50%) to afford (R,E)-N-(4-(3-((5-chloro-4-methoxypyrimidin-2-yl)amino)pyrrolidine-1-carbonyl)phenyl)-4-(3,3-difluoropiperidin-1-yl)but-2-enamide (28 mg, 18%) as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6): 1.64-1.69 (m, 2H), 1.85-2.15 (m, 4H), 2.43-2.49 (m, 2H), 2.65-2.70 (m, 2H), 3.22-3.24 (d, J = 8.0 Hz, 2H), 3.35-3.79 (m, 4H), 3.85-3.94 (m, 3H), 4.26-4.27 (m, 1H), 6.26-6.30 (m, 1H), 6.73-6.78 (m, 1H), 7.49-7.52 (m, 2H), 7.68 -7.72 (m, 3H), 8.07-8.14 (m, 1H), 10.24 (s, 1H). [M+H] Calc'd for$C_{25}H_{29}ClF_2N_6O_3$, 535.2; Found, 535.2.

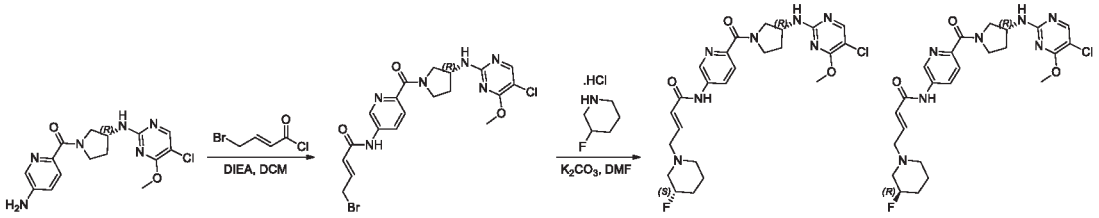
Example 174: Synthesis of (R,E)-N-(6-(3-((5-chloro-4-methoxypyrimidin-2-yl)amino)pyrrolidine-1-carbonyl)pyridin-3-yl)-4-morpholinobut-2-enamide



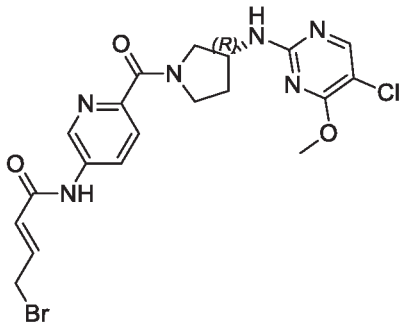
[00664] A solution of (R,E)-4-bromo-N-(6-(3-((5-chloro-4-methoxypyrimidin-2-yl)amino)pyrrolidine-1-carbonyl)pyridin-3-yl)but-2-enamide (90 mg, 0.18 mmol), morpholine (32 mg, 0.36 mmol) and DIEA (94 mg, 0.73 mmol) in DCM (5 mL) was stirred at RT for 16h. The mixture was concentrated and the residue was purified by *prep*-HPLC to afford (R,E)-N-(6-(3-((5-chloro-4-methoxypyrimidin-2-yl)amino)pyrrolidine-1-carbonyl)pyridin-3-yl)-4-morpholinobut-2-enamide (6.8 mg, 8%) as a brown solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.93-1.99 (m, 1H), 2.12-2.19 (m, 1H), 2.36-2.40 (m, 4H), 3.14-3.15 (m, 4H), 3.49-3.61 (m, 4H), 3.64-3.82 (m, 2H), 3.88-3.94 (m, 3H), 4.32-4.38 (m, 1H), 6.28-6.33 (m, 1H), 6.76-6.84 (m, 1H), 7.65-7.77 (m, 2H), 8.09-8.20 (m,

2H), 8.80 (dd, ***J*** = 2.4, 16.4 Hz, 1H), 10.47 (d, ***J*** = 6.0 Hz, 1H). [M+H] Calc'd for $C_{46}H_{57}BrCl_2N_{14}O_8$, 502.2; Found, 502.2.

Example 175 & 176: Synthesis of (E)-N-(6-((R)-3-((5-chloro-4-methoxypyrimidin-2-yl)amino)pyrrolidine-1-carbonyl)pyridin-3-yl)-4-((S)-3-fluoropiperidin-1-yl)but-2-enamide & (E)-N-(6-((R)-3-((5-chloro-4-methoxypyrimidin-2-yl)amino)pyrrolidine-1-carbonyl)pyridin-3-yl)-4-((R)-3-fluoropiperidin-1-yl)but-2-enamide

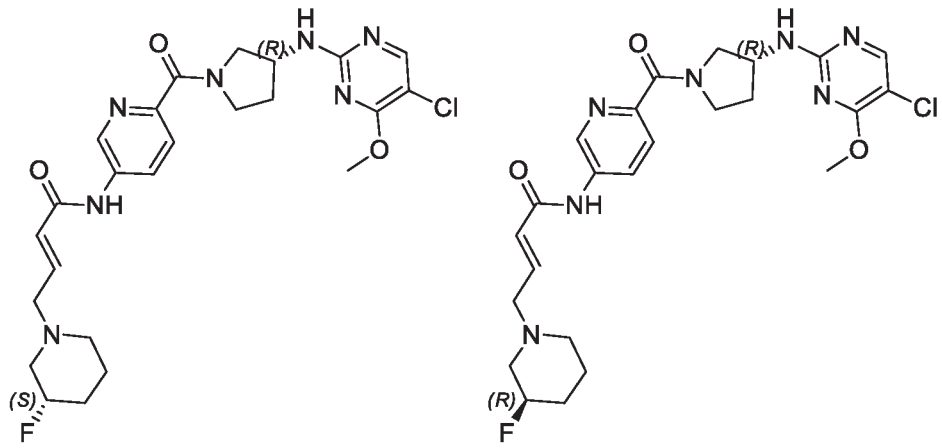


Step 1: (R,E)-4-bromo-N-(6-(3-((5-chloro-4-methoxypyrimidin-2-yl)amino)pyrrolidine-1-carbonyl)pyridin-3-yl)but-2-enamide



[00665] To a solution of (R)-(5-aminopyridin-2-yl)(3-((5-chloro-4-methoxypyrimidin-2-yl)amino)pyrrolidin-1-yl)methanone (1.0 g, 2.9 mmol) and DIEA (1.1 g, 8.7 mmol) in DCM (50 mL) was added a solution of (E)-4-bromobut-2-enoyl chloride (1.1 g, 5.8 mmol) in DCM (10 mL) in an ice-bath and the reaction mixture was stirred at 0°C for 10 min. The reaction mixture was fitered and concentrated and the residue was purified by silica gel chromatography (PE:EA = 1:1) to afford (R,E)-4-bromo-N-(6-(3-((5-chloro-4-methoxypyrimidin-2-yl)amino)pyrrolidine-1-carbonyl)pyridin-3-yl)but-2-enamide (500 mg, 36%) as a white solid. [M+H] Calc'd for $C_{19}H_{20}BrClN_6O_3$, 495.0; Found, 495.0.

Step2: Synthesis of (E)-N-(6-((R)-3-((5-chloro-4-methoxypyrimidin-2-yl)amino)pyrrolidine-1-carbonyl)pyridin-3-yl)-4-((S)-3-fluoropiperidin-1-yl)but-2-enamide and (E)-N-(6-((R)-3-((5-chloro-4-methoxypyrimidin-2-yl)amino)pyrrolidine-1-carbonyl)pyridin-3-yl)-4-((R)-3-fluoropiperidin-1-yl)but-2-enamide

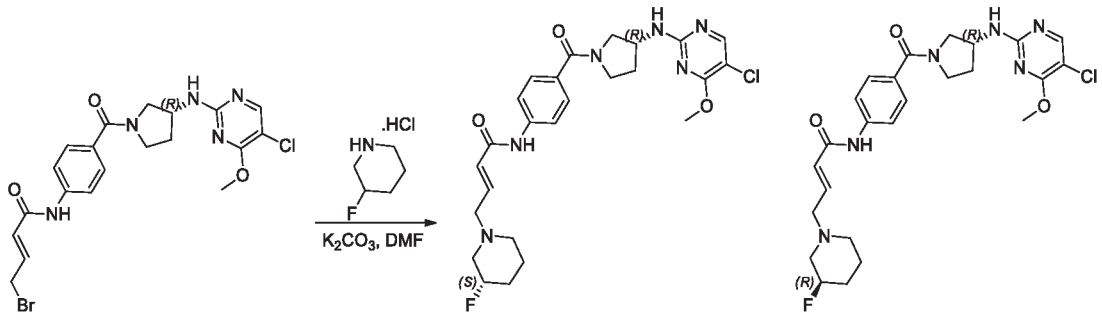


[00666] A solution of (R,E)-4-bromo-N-(6-(3-((5-chloro-4-methoxypyrimidin-2-yl)amino)pyrrolidine-1-carbonyl)pyridin-3-yl)but-2-enamide (200 mg, 0.4 mmol), 3-fluoropiperidine HCl salt (225 mg, 1.6 mmol) and K_2CO_3 (442 mg, 3.2 mmol) in DMF (20 mL) was stirred at RT for 16h. The mixture was concentrated *in vacuo* and the residue was purified by *prep*-HPLC (120 mg, 58%) and chiral separation (IE: 4.6mm*250mm 5um; Method Filename: MeOH-DCM-DEA = 80-20-0.2) to afford (E)-N-(6-((R)-3-((5-chloro-4-methoxypyrimidin-2-yl)amino)pyrrolidine-1-carbonyl)pyridin-3-yl)-4-((S)-3-fluoropiperidin-1-yl)but-2-enamide (56.9 mg, Rt = 10.227 min) and (E)-N-(6-((R)-3-((5-chloro-4-methoxypyrimidin-2-yl)amino)pyrrolidine-1-carbonyl)pyridin-3-yl)-4-((R)-3-fluoropiperidin-1-yl)but-2-enamide (40.5 mg, Rt = 16.573 min) as a white solid.

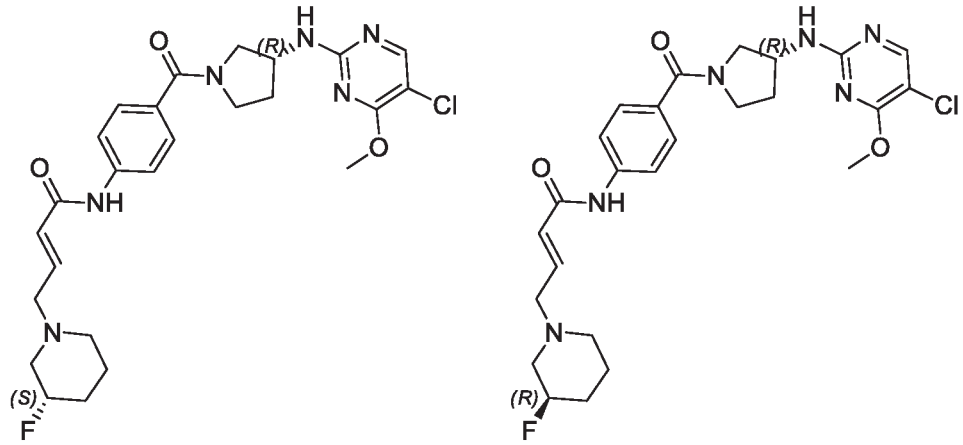
Rt = 10.227 min: ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.51-1.52 (m, 2H), 1.72-1.94 (m, 4H), 2.13-2.43 (m, 3H), 2.66-2.71 (m, 1H), 3.17-3.19 (m, 2H), 3.48-3.69 (m, 3H), 3.77-4.02 (m, 4H), 4.35-4.37 (m, 1H), 4.58-4.71 (m, 1H), 6.26-6.30 (m, 1H), 6.78-6.81 (m, 1H), 7.70-7.79 (m, 2H), 8.09-8.21 (m, 2H), 8.78-8.82 (m, 1H), 10.48-10.50 (m, 1H). [M+H] Calc'd for $C_{24}H_{29}ClFN_7O_3$, 518.2; Found, 518.2.

Rt = 16.573 min: ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.49-1.51 (m, 2H), 1.74-1.96 (m, 4H), 2.13-2.43 (m, 3H), 2.66-2.69 (m, 1H), 3.17-3.19 (m, 2H), 3.52-3.69 (m, 3H), 3.77-3.93 (m, 4H), 4.35-4.37 (m, 1H), 4.60-4.72 (m, 1H), 6.27-6.31 (m, 1H), 6.77-6.81 (m, 1H), 7.67-7.79 (m, 2H), 8.09-8.21 (m, 2H), 8.78-8.83 (m, 1H), 10.48-10.50 (m, 1H). [M+H] Calc'd for $C_{24}H_{29}ClFN_7O_3$, 518.2; Found, 518.2.

Example 177 & 178: Synthesis of (E)-N-(4-((R)-3-((5-chloro-4-methoxypyrimidin-2-yl)amino)pyrrolidine-1-carbonyl)phenyl)-4-((S)-3-fluoropiperidin-1-yl)but-2-enamide & (E)-N-(4-((R)-3-((5-chloro-4-methoxypyrimidin-2-yl)amino)pyrrolidine-1-carbonyl)phenyl)-4-((R)-3-fluoropiperidin-1-yl)but-2-enamide



Step1: (E)-N-(4-((R)-3-((5-chloro-4-methoxypyrimidin-2-yl)amino)pyrrolidine-1-carbonyl)phenyl)-4-((S)-3-fluoropiperidin-1-yl)but-2-enamide & (E)-N-(4-((R)-3-((5-chloro-4-methoxypyrimidin-2-yl)amino)pyrrolidine-1-carbonyl)phenyl)-4-((R)-3-fluoropiperidin-1-yl)but-2-enamide

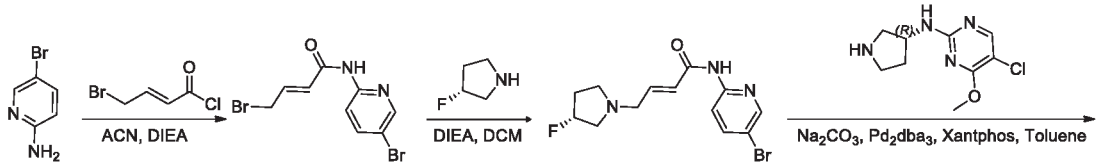


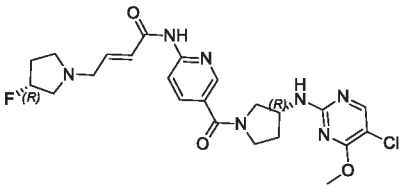
[00667] A solution of (R,E)-4-bromo-N-(4-(3-((5-chloro-4-methoxypyrimidin-2-yl)amino)pyrrolidine-1-carbonyl)phenyl)but-2-enamide (400 mg, 0.8 mmol), 3-fluoropiperidine HCl salt (445 mg, 3.2 mmol) and K_2CO_3 (883 mg, 6.4 mmol) in DMF (20 mL) was stirred at RT for 16h. The mixture was concentrated and the residue was purified by prep-HPLC (60 mg, 14%) and chiral separation (IG: 4.6mm*250mm 5um; Method Filename: MeOH-DCM-DEA = 85-15-0.2) to afford (E)-N-(4-((R)-3-((5-chloro-4-methoxypyrimidin-2-yl)amino)pyrrolidine-1-carbonyl)phenyl)-4-((S)-3-fluoropiperidin-1-yl)but-2-enamide (19.7 mg, Rt = 10.249 min) and (E)-N-(4-((R)-3-((5-chloro-4-methoxypyrimidin-2-yl)amino)pyrrolidine-1-carbonyl)phenyl)-4-((R)-3-fluoropiperidin-1-yl)but-2-enamide (19 mg, Rt = 17.114 min) as a white solid.

Rt = 10.249 min: ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.51-1.52 (m, 2H), 1.72-1.94 (m, 4H), 2.10-2.41 (m, 3H), 2.67-2.69 (m, 1H), 3.15-3.17 (m, 2H), 3.34-3.62 (m, 4H), 3.77 -3.93(m, 3H), 4.24-4.40 (m, 1H), 4.59-4.71 (m, 1H), 6.25-6.29 (m, 1H), 6.73-6.76 (m, 1H), 7.47-7.50 (m, 2H), 7.67-7.72 (m, 3H), 8.07-8.15 (m, 1H), 10.24-10.25 (m, 1H). [M+H] Calc'd for $C_{25}H_{30}ClFN_6O_3$, 517.2; Found, 517.2.

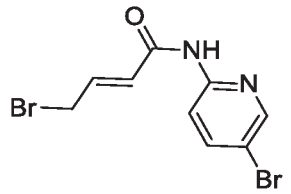
Rt = 17.114 min: ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.48-1.51 (m, 2H), 1.71-1.96 (m, 4H), 2.13-2.43 (m, 3H), 2.67-2.69 (m, 1H), 3.15-3.17 (m, 2H), 3.33-3.62 (m, 4H), 3.77 -3.93(m, 3H), 4.26-4.40 (m, 1H), 4.61-4.71 (m, 1H), 6.25-6.29 (m, 1H), 6.73-6.75 (m, 1H), 7.47-7.53 (m, 2H), 7.67-7.72 (m, 3H), 8.07-8.16 (m, 1H), 10.24-10.25 (m, 1H). [M+H] Calc'd for $C_{25}H_{30}ClFN_6O_3$, 517.2; Found, 517.2.

Example 179: Synthesis of (E)-N-(5-((R)-3-((5-chloro-4-methoxypyrimidin-2-yl)amino)pyrrolidine-1-carbonyl)pyridin-2-yl)-4-((R)-3-fluoropyrrolidin-1-yl)but-2-enamide



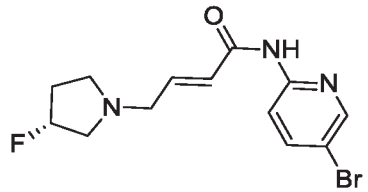


Step 1: (E)-4-bromo-N-(5-bromopyridin-2-yl)but-2-enamide



[00668] To a solution of 5-bromopyridin-2-amine (346 mg, 2.0 mmol) and DIEA (774 mg, 6.0 mmol) in CH_3CN (10 mL) was added (E)-4-bromobut-2-enoyl chloride (550 mg, 3.0 mmol) in an ice-bath and the reaction mixture was stirred at 0°C for 10 min.The reaction mixture was fitered and concentrated. The residue was purified by silica gel chromatography (PE:EA = 5:1) to afford (E)-4-bromo-N-(5-bromopyridin-2-yl)but-2-enamide (280 mg, 44%) as white solid. [M+H] Calc'd for $C_9H_8Br_2N_2O$, 318.9; Found, 318.9.

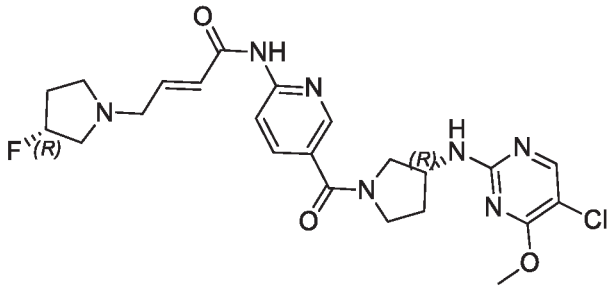
Step 2: Synthesis of (R,E)-N-(5-bromopyridin-2-yl)-4-(3-fluoropyrrolidin-1-yl)but-2-enamide



[00669] To a solution of (E)-4-bromo-N-(5-bromopyridin-2-yl)but-2-enamide (280 mg, 0.88 mmol) and (R)-3-fluoropyrrolidine (156 mg, 1.75 mmol) in DCM (20 mL) was added DIEA (340 mg, 2.64 mmol) in an ice-bath. The reaction mixture was fitered and concentrated and the residue was purified by silica gel chromatography (PE:EA = 5:1) to afford (R,E)-N-(5-bromopyridin-2-yl)-4-(3-

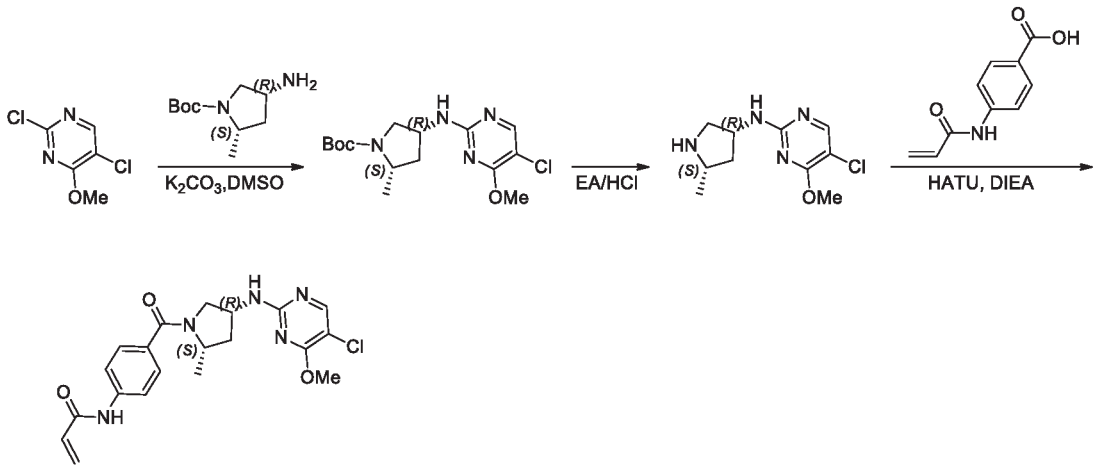
fluoropyrrolidin-1-yl)but-2-enamide (180 mg, 60%) as a yellow solid. [M+H] Calc'd for $C_{13}H_{15}BrFN_3O$, 328.0; Found, 328.0.

Step 3: (E)-N-(5-((R)-3-((5-chloro-4-methoxypyrimidin-2-yl)amino)pyrrolidine-1-carbonyl)pyridin-2-yl)-4-((R)-3-fluoropyrrolidin-1-yl)but-2-enamide

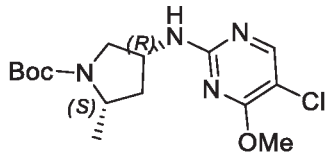


[00670] A solution of (R,E)-N-(5-bromopyridin-2-yl)-4-(3-fluoropyrrolidin-1-yl)but-2-enamide (70 mg, 0.2 mmol), (R)-5-chloro-4-methoxy-N-(pyrrolidin-3-yl)pyrimidin-2-amine (73 mg, 0.3 mmol), Na_2CO_3 (64 mg, 0.6 mmol), Pd_2dba_3 (73 mg, 0.08 mmol) and Xantphos (46 mg, 0.08 mmol) in toluene (10 mL) was stirred at 110°C for 16h under CO. The mixture was concentrated. The residue was purified by prep-HPLC to afford HCOOH salt of (E)-N-(5-((R)-3-((5-chloro-4-methoxypyrimidin-2-yl)amino)pyrrolidine-1-carbonyl)pyridin-2-yl)-4-((R)-3-fluoropyrrolidin-1-yl)but-2-enamide (5.5 mg, 6%) as a yellow solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.87-1.91 (m, 2H), 2.13-2.16 (m, 2H), 2.33-2.34 (m, 1H), 2.60-2.67 (m, 1H), 2.81-2.83 (m, 2H), 3.53-3.69 (m, 6H), 3.86 -3.93 (m, 3H), 4.30-4.43 (m, 1H), 5.14-5.28 (m, 1H), 6.46-6.49 (m, 1H), 6.81-6.86 (m, 1H), 7.71-7.73 (m, 1H), 7.95-7.99 (m, 1H), 8.08-8.24 (m, 2H), 8.30-8.32 (m, 1H), 8.50-8.52 (m, 1H), 10.82-10.84 (m, 1H). [M+H] Calc'd for $C_{23}H_{27}ClFN_7O_3$, 504.2; Found, 504.2.

Example 180: Synthesis of N-(4-((2S,4R)-4-((5-chloro-4-methoxypyrimidin-2-yl)amino)-2-methylpyrrolidine-1-carbonyl)phenyl)acrylamide

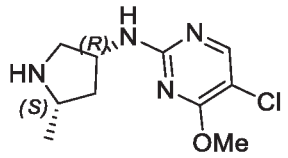


Step 1: (2S,4R)-tert-butyl 4-((5-chloro-4-methoxypyrimidin-2-yl)amino)-2-methylpyrrolidine-1-carboxylate



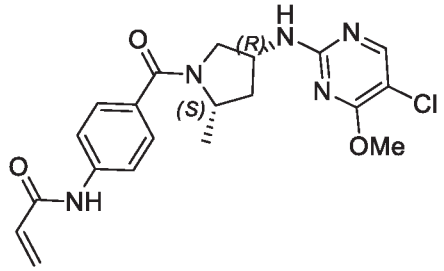
[00671] A solution of (2S,4R)-tert-butyl 4-amino-2-methylpyrrolidine-1-carboxylate (200 mg, 1.0 mmol), 2,5-dichloro-4-methoxypyrimidine (358 mg. 2.0 mmol) and K_2CO_3 (226 mg, 2.0 mmol) in DMSO (10 mL) was stirred at RT for 2 hrs. The reaction mixture was diluted with water (30 mL) and extracted with EA (20 mL*3). The combined organic layers were washed with water (50 mL) and brine (50 mL), dried over Na_2SO_4, filtered and concentrated *in vacuo*. The residue was purified by silica gel chromatography (PE:EA = 1:1) to afford (2S,4R)-tert-butyl 4-((5-chloro-4-methoxypyrimidin-2-yl)amino)-2-methylpyrrolidine-1-carboxylate (100 mg, 30%) as a white solid. [M+H] Calc'd for $C_{15}H_{23}ClN_4O_3$, 343.1; Found,343.1

Step 2: Synthesis of 5-chloro-4-methoxy-N-((3R,5S)-5-methylpyrrolidin-3-yl)pyrimidin-2-amine



[00672] A solution of (2S,4R)-tert-butyl 4-((5-chloro-4-methoxypyrimidin-2-yl)amino)-2-methylpyrrolidine-1-carboxylate (100 mg, 0.3 mmol) in EA/HCl (10 mL, 3 M) was stirred at RT for 2 hrs. The reaction mixture was concentrated to afford 5-chloro-4-methoxy-N-((3R,5S)-5-methylpyrrolidin-3-yl)pyrimidin-2-amine (73 mg, 100%) as a white solid. [M+H] Calc'd for $C_{10}H_{15}ClN_4O$, 243.1; Found, 243.1

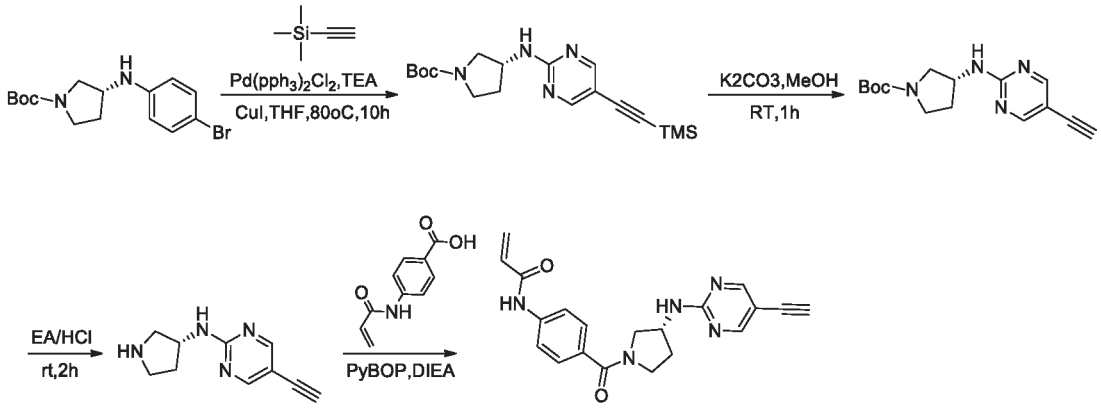
Step 3: N-(4-((2S,4R)-4-((5-chloro-4-methoxypyrimidin-2-yl)amino)-2-methylpyrrolidine-1-carbonyl)phenyl)acrylamide



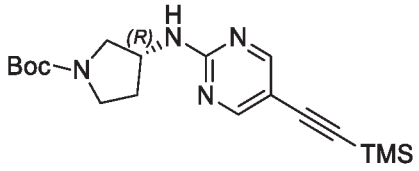
[00673] A solution of 5-chloro-4-methoxy-N-((3R,5S)-5-methylpyrrolidin-3-yl)pyrimidin-2-amine (73 mg, 0.3 mmol), 4-acrylamidobenzoic acid (58 mg, 0.3 mmol), HATU (125 mg, 0.33 mmol) and DIEA (116 mg, 0.9 mmol) in DMF (10 mL) was stirred at RT for 16h. The mixture was concentrated and purified by prep-HPLC to afford N-(4-((2S,4R)-4-((5-chloro-4-methoxypyrimidin-2-yl)amino)-2-methylpyrrolidine-1-carbonyl)phenyl)acrylamide (10.1 mg, 8%) as a white solid. ^{1}H NMR (400

MHz, DMSO-d_6): δ 1.29-1.31 (m, 3H), 1.65-1.67 (m, 1H), 2.45-2.46 (m, 1H), 3.70-3.83 (m, 5H), 4.08-4.17 (m, 2H), 5.79 (dd, J = 1.6, 10.0 Hz, 1H), 6.25-6.30 (m, 1H), 6.41-6.48 (m, 1H), 7.49-7.51 (m, 2H), 7.70-7.72 (m, 3H), 8.07 (s, 1H), 10.33 (s, 1H). [M+H] Calc'd for $C_{20}H_{22}ClN_5O_3$, 416.1; Found, 416.1.

Example 181: (R)-N-(4-(3-((5-ethynylpyrimidin-2-yl)amino)pyrrolidine-1-carbonyl)phenyl)acrylamide

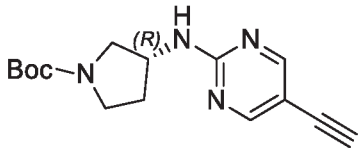


Step 1:(R)-tert-butyl3-((5-((trimethylsilyl)ethynyl)pyrimidin-2-yl)amino)pyrrolidine-1-carboxylate



[00674] A solution of (R)-tert-butyl 3-((4-bromophenyl)amino)pyrrolidine-1-carboxylate (2.0 g, 5.8 mmmol), ethynyl trimethylsilane (1.1 g, 11.7 mmol), CuI (33 mg, 0.2 mmol) and $Pd(PPh_3)_2Cl_2$ (205 mg, 0.3 mmol) in TEA (20 mL) and THF (20 mL) was stirred at 80°C for 10h under N_2. The reaction mixture was cooled, diluted with water (50 mL) and extracted with EA (100 mL*2). The combined organic layers were washed with brine (50 mL), dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (PE/EA = 5/1) to give (R)-*tert*-butyl 3-((5-((trimethylsilyl)ethynyl)pyrimidin-2-yl)amino)pyrrolidine-1-carboxylate (1.0 g, 47%). [M+H] MS Calc'd $C_{18}H_{28}N_4O_2Si$, 361.1; Found: 361.1.

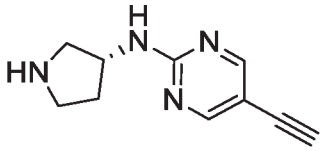
Step 2:(R)-tert-butyl 3-((5-ethynylpyrimidin-2-yl)amino)pyrrolidine-1-carboxylate



[00675] To a solution of (R)-tert-butyl 3-((5-((trimethylsilyl)ethynyl)pyrimidin-2-yl)amino)pyrrolidine-1-carboxylate (1.0 g, 2.8 mmol) in MeOH (20 mL) was added K_2CO_3 (766 mg 5.5 mmol) in an ice-

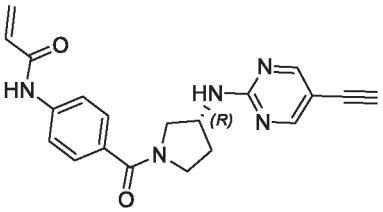
bath and the mixture was stirred at RT for 1h. Filtered and concentrated *in vacuo* to give (R)-tert-butyl 3-((5-ethynylpyrimidin-2-yl)amino)pyrrolidine-1-carboxylate (435 mg, 54%) as a white solid. [M+H] MS Calc'd: $C_{15}H_{20}N_4O_2$, 289.1; Found: 289.1.

Step 3: (R)-5-ethynyl-N-(pyrrolidin-3-yl)pyrimidin-2-amine



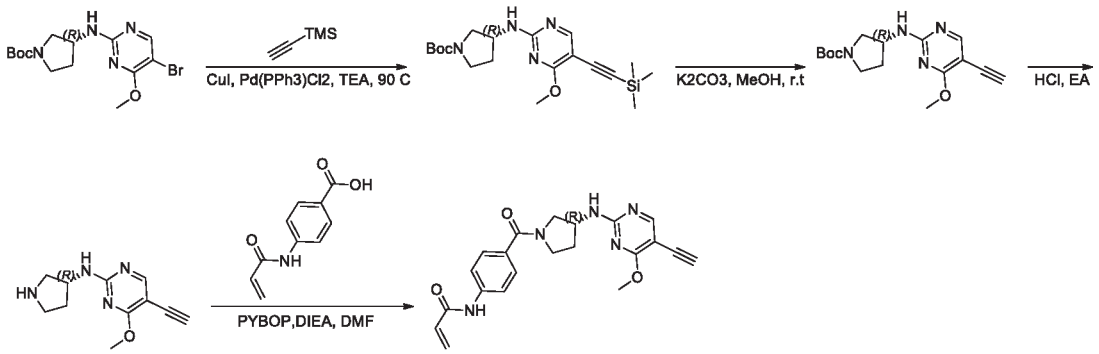
[00676] A solution of (R)-tert-butyl 3-((5-ethynylpyrimidin-2-yl)amino)pyrrolidine-1-carboxylate (435 mg, 1.51 mmol) in HCl/EA (15 mL, 3 M) was stirred at RT for 1h. The mixture was concentrated *in vacuo* to give (R)-5-ethynyl-N-(pyrrolidin-3-yl)pyrimidin-2-amine HCl salt (283 mg, crude) as brown thick liquid. [M+H] MS Calc'd: $C_{10}H_{12}N_4$,189.1; Found: 189.1.

Step 4:(R)-N-(4-(3-((5-ethynylpyrimidin-2-yl)amino)pyrrolidine-1-carbonyl)phenyl)acrylamide

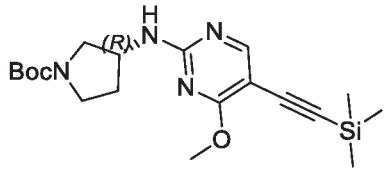


[00677] A mixture of (R)-5-ethynyl-N-(pyrrolidin-3-yl)pyrimidin-2-amine HCl salt (260 mg, 1.35 mmol), 4-acrylamidobenzoic acid (281 mg, 1.49 mmol), PyBOP (777 mg, 1.49 mmol) and DIEA (871 mg, 6.75 mmol) in DMF (15 mL) was stirred at RT overnight. The reaction mixture was concentrated and the residue was purified by prep-HPLC to afford (R)-N-(4-(3-((5-ethynylpyrimidin-2-yl)amino)pyrrolidine-1-carbonyl)phenyl)acrylamide (28.9 mg, 5.8%) as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6): 1.89-1.99 (m, 1H), 2.14-2.16 (m, 1H), 3.43-3.53 (m, 2H), 3.64-3.80 (m, 2H), 4.22-4.49 (m, 2H), 5.78 (d, J = 10.0 Hz, 1H), 6.25-6.30 (m, 1H), 6.43-6.45 (m, 1H), 7.50 (t, J = 9.2 Hz, 2H), 7.70 (t, J = 9.2 Hz, 2H), 7.98-8.00 (m, 1H), 8.38-8.44 (m, 2H), 10.29 (s, 1H). [M+H] Calc'd for $C_{20}H_{19}N_5O_2$, 362.1; Found, 362.1.

Example 182: (R)-tert-butyl (R)-N-(4-(3-((5-ethynyl-4-methoxypyrimidin-2-yl)amino)pyrrolidine-1-carbonyl)phenyl)acrylamide

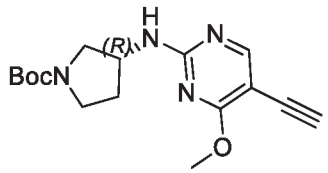


Step 1: (R)-tert-butyl 3-((4-methoxy-5-((trimethylsilyl)ethynyl)pyrimidin-2-yl)amino)pyrrolidine-1-carboxylateboxylate



[00678] A solution of (R)-tert-butyl 3-((5-bromo-4-methoxypyrimidin-2-yl)amino)pyrrolidine-1-carboxylate (1.0 g, 2.7 mmmol), ethynyltrimethylsilane(1.1 g, 10.7 mmol), CuI (152 mg, 0.8 mmol), $Pd(PPh_3)Cl_2$ (180 mg, 0.3 mmol) in TEA (20 mL) was stirred at 90°C for 2h. The mixture was cooled, diluted with water (50 mL) and extracted with EA (50 mL*2). The combined organic layers were washed with brine (50 mL), dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (PE/EA = 2/1) to give (R)-tert-butyl 3-((4-methoxy-5-((trimethylsilyl)ethynyl)pyrimidin-2-yl)amino)pyrrolidine-1-carboxylateboxylate (500 mg, 47%). [M+H] MS Calc'd $C_{19}H_{30}N_4O_3Si$, 391.2; Found: 391.2.

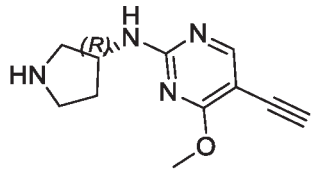
Step 2: (R)-tert-butyl 3-((5-ethynyl-4-methoxypyrimidin-2-yl)amino)pyrrolidine-1-carboxylate



[00679] A solution of (R)-tert-butyl 3-((4-methoxy-5-((trimethylsilyl)ethynyl)pyrimidin-2-yl)amino)pyrrolidine-1-carboxylateboxylate (500 mg, 2.5 mmol) and K_2CO_3 (690 mg, 5.0 mmol) in MeOH (30 mL) was stirred at RT for 3h. The reaction mixture was filtered and concentrated under vacuum to give (R)-tert-butyl 3-((5-ethynyl-4-methoxypyrimidin-2-yl)amino)pyrrolidine-1-carboxylate (200 mg, 66%) as a yellow solid.

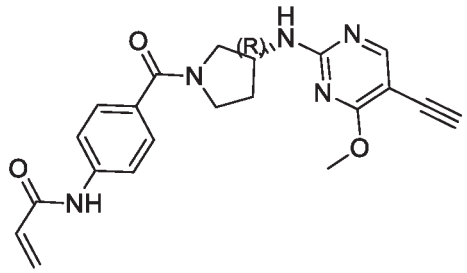
[M +H] MS Calc'd: $C_{16}H_{22}N_4O_3$ 319.1; Found: 319.1.

Step 3: (R)-5-ethynyl-4-methoxy-N-(pyrrolidin-3-yl)pyrimidin-2-amine



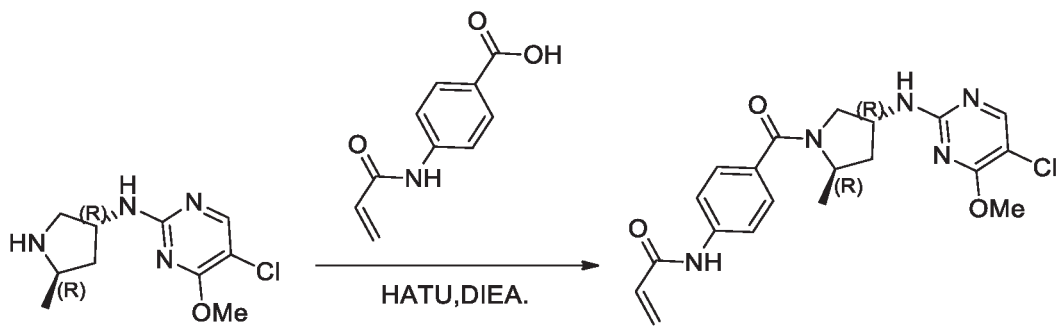
[00680] A solution of (R)-tert-butyl 3-((5-ethynyl-4-methoxypyrimidin-2-yl)amino)pyrrolidine-1-carboxylate (180 mg, 0.45 mmol) in HCl/EA (15 mL, 3M) was stirred at rt for 3h. The reaction mixture was then concentrated under vacuum to give product (R)-5-ethynyl-4-methoxy-N-(pyrrolidin-3-yl)pyrimidin-2-amine (100 mg, 75%) as a yellow solid. [M+H] MS Calc'd: $C_{11}H_{14}N_4O$,219.1; Found: 219.1.

Step 4: (R)-N-(4-(3-((5-ethynyl-4-methoxypyrimidin-2-yl)amino)pyrrolidine-1-carbonyl)phenyl)acrylamide



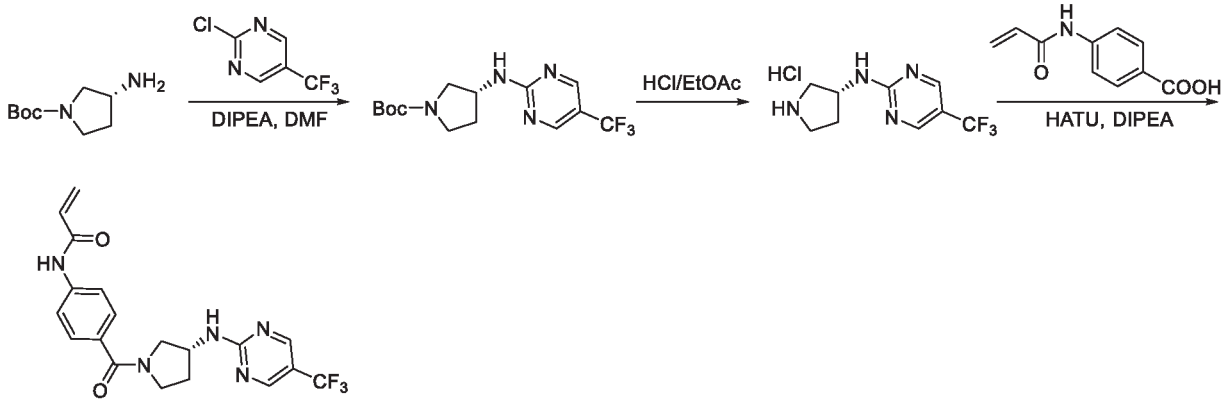
[00681] A mixture of (R)-5-ethynyl-4-methoxy-N-(pyrrolidin-3-yl)pyrimidin-2-amine HCl salt (100 mg, 0.34 mmol), 4-acrylamidobenzoic acid (78 mg, 0.41 mmol), PyBOP (213 mg, 0.41 mmol) and DIEA (131 mg, 1.02 mmol) in DMF (15 mL) was stirred at RT for overnight. The reaction mixture was concentrated and the residue was purified by prep-HPLC to afford (R)-N-(4-(3-((5-ethynyl-4-methoxypyrimidin-2-yl)amino)pyrrolidine-1-carbonyl)phenyl)acrylamide (4.5 mg, 3%) as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6): 1.90-2.13 (m, 2H), 3.31-3.90 (m, 7H), 4.18 (d, J = 13.2 Hz, 1H), 4.32 (s, 0.5H), 4.85 (s, 0.5H), 5.78 (d, J = 10.0 Hz, 1H), 6.25 (s, 0.5H), 6.30 (s, 0.5H), 6.36-6.41 (m, 1H), 7.50 (t, J = 8.8 Hz, 2H), 7.71 (t, J = 8.8 Hz, 2H), 7.84-8.00 (m, 1H), 8.15-8.16 (m, 1H),10.29 (s, 1H). [M+H] Calc'd for $C_{21}H_{21}N_5O_3$, 392.2; Found, 392.2.

Example 183: N-(4-((2R,4R)-4-((5-chloro-4-methoxypyrimidin-2-yl)amino)-2-methylpyrrolidine-1-carbonyl)phenyl)acrylamide

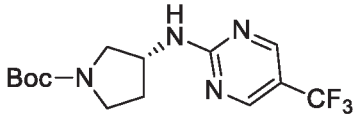


[00682] A mixture of 5-chloro-4-methoxy-N-((3R,5R)-5-methylpyrrolidin-3-yl)pyrimidin-2-amine TFA salt (400 mg, 1.65 mmol), 4-acrylamidobenzoic acid (315 mg, 1.65 mmol), HATU (760 mg, 1.98 mmol) and DIEA (660 mg, 5 mmol) in DMF (10 mL) was stirred at RT for overnight. The reaction mixture was concentrated and the residue was purified by prep-HPLC to afford N-(4-((2R,4R)-4-((5-chloro-4-methoxypyrimidin-2-yl)amino)-2-methylpyrrolidine-1-carbonyl)phenyl)acrylamide (3.8 mg, 0.5%) as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6): 1.30-1.32 (m, 3H), 1.85-1.87 (m, 1H), 2.16-2.14 (m, 1H), 3.37-3.38 (m, 1H), 3.89 (s, 4H), 4.26-4.37 (m, 2H) 5.79-5.83 (m, 1H), 6.32-6.46 (m, 2H), 7.49 (d, J = 11.2 Hz, 2H), 7.70-7.73 (m, 3H), 8.09 (s, 1H), 10.34 (s, 1H). [M+H] Calc'd for $C_{20}H_{22}ClN_5O_3$, 416.1; Found, 416.1.

Example 184: Synthesis of (R)-N-(4-(3-((5-(trifluoromethyl)pyrimidin-2-yl)amino)pyrrolidine-1-carbonyl)phenyl)acrylamide

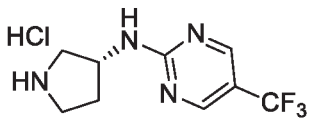


Step 1: (R)-tert-butyl 3-((5-(trifluoromethyl)pyrimidin-2-yl)amino)pyrrolidine-1-carboxylate



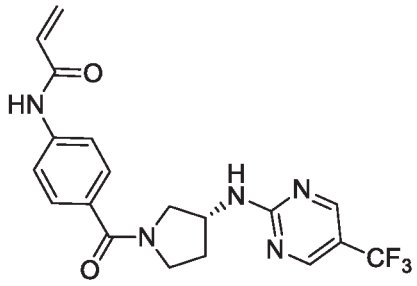
[00683] A mixture of 2-chloro-5-(trifluoromethyl)pyrimidine (293 mg, 1.61 mmol), (R)-tert-butyl 3-aminopyrrolidine-1-carboxylate (300 mg, 1.61 mmol) and DIPEA (623 mg, 4.83 mmol) in DMF (3.0 mL) was stirred at 40 °C for 2.5 hours. The reaction mixture was diluted with H_2O (30 mL) and extracted with EtOAc (30 mL*2). The combined organic phases were washed with water (40 mL*2), brine (40 mL), dried over Na_2SO_4, filtered and concentrated. The residue was purified by silica gel column (petroleum ether/EtOAc = 5/1) to give (R)-tert-butyl 3-((5-(trifluoromethyl)pyrimidin-2-yl)amino)pyrrolidine-1-carboxylate (502 mg, 94%). [M+H] MS Calc'd $C_{14}H_{19}F_3N_4O_2$, 333.2; Found: 333.2.

Step 2: (R)-N-(pyrrolidin-3-yl)-5-(trifluoromethyl)pyrimidin-2-amine



[00684] A mixture of (R)-tert-butyl 3-((5-(trifluoromethyl)pyrimidin-2-yl)amino)pyrrolidine-1-carboxylate (502 mg, 1.51 mmol) in HCl/EtOAc (10.0 mL, 4M in EtOAc) was stirred at RT for 1 hour. The reaction mixture was concentrated under reduced pressure to afford the crude product (R)-N-(pyrrolidin-3-yl)-5-(trifluoromethyl)pyrimidin-2-amine hydrochloride HCl salt (390 mg, 95%) which was used in the next step without any further purification. [M+H] MS Calc'd $C_9H_{11}F_3N_4$, 233.1; Found: 233.1.

Step 3: (R)-N-(4-(3-((5-(trifluoromethyl)pyrimidin-2-yl)amino)pyrrolidine-1-carbonyl)phenyl)acrylamide



[00685] To a mixture of (R)-N-(pyrrolidin-3-yl)-5-(trifluoromethyl)pyrimidin-2-amine HCl salt (195 mg, 0.73 mmol), 4-propionamidobenzoic acid (139 mg, 0.73 mmol) and DIPEA (471 mg, 3.65 mmol) in DMF (5.0 mL) was added HATU (334 mg, 0.88 mmol) slowly and the mixture was stirred at RT overnight. The mixture was diluted with H_2O (30 mL), then extracted with EtOAc (30 mL*2). The organic phases were washed with water (30 mL*2) and brine (30 mL), dried over Na_2SO_4, filtered and concentrated *in vacuo*. The residue was purified by *Prep*-HPLC to give (R)-N-(4-(3-((5-(trifluoromethyl)pyrimidin-2-yl)amino)pyrrolidine-1-carbonyl)phenyl)acrylamide (43.5 mg, 15%). ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.89-2.04 (m, 1H), 2.16-2.21 (m, 1H), 3.36-3.83 (m, 4H), 4.36-4.53 (m, 1H), 5.78 (d, J = 10.0 Hz, 1H), 6.28 (d, J = 16.9 Hz, 1H), 6.41-6.48 (m, 1H), 7.49-7.54 (m, 2H), 7.68-7.74 (m, 2H), 8.41 (s, 1H), 8.61-8.70 (m, 2H), 10.30 (brs, 1H). [M+H] MS Calc'd $C_{19}H_{18}F_3N_5O_2$, 406.1; Found: 406.0.

II. Biological Evaluation

Example 1 – Assay condition A (thiol containing conditions)

[00686] *Objective:* The IC_{50} profile of test compounds was determined using three protein kinases. IC_{50} values were measured by testing 10 concentrations (1 x 10^{-04}M, 3 x 10^{-05}M, 1 x 10^{-05}M, 3 x 10^{-06}M, 1 x 10^{-06}M, 3 x 10^{-07}M, 1 x 10^{-07}M, 3 x 10^{-08}M, 1 x 10^{-08}M, and 3 x 10^{-09}M) of each compound in singlicate.

[00687] *Test compounds:* The compounds were provided as pre-weighed powders in vials. The compounds were dissolved to 1 x 10^{-02}M by adding DMSO. 100 µl of each of the resulting stock solutions were transferred into column 2 of four 96 well "master plates".

[00688] Prior to testing, the 1 x 10^{-02}M stock solutions in column 2 of the master plates were subjected to a serial, semi-logarithmic dilution using 100 % DMSO as a solvent. This resulted in 10 distinct concentrations, with a dilution endpoint of 3 x 10^{-07}M/100 % DMSO in column 12. Column 1 and 7 were filled with 100 % DMSO as controls. Subsequently, 2 x 10 µl from each well of the serial diluted copy plates were aliquoted with a 96 channel pipettor into two identical sets of "compound dilution plates".

[00689] In the process, 90 µl H_2O were added to each well of a set of compound dilution plates. To minimize potential precipitation, the H_2O was added to each plate only a few minutes before the transfer of the compound solutions into the assay plates. Each plate was shaken thoroughly, resulting in a "compound dilution plate/ 10 % DMSO".

[00690] For the assays, 5 µl solution from each well of the compound dilution plates/10 % DMSO were transferred into the assay plates. The final volume of the assay was 50 µl. All compounds were tested at 10 final assay concentrations in the range from 1 x 10^{-04}M to 3 x 10^{-09}M, in singlicate. The final DMSO concentration in the reaction cocktails was 1 % in all cases.

[00691] *Recombinant protein kinases:* All protein kinases were expressed in Sf9 insect cells or in E.coli as recombinant GST-fusion proteins or His-tagged proteins, either as full-length or enzymatically active fragments. All kinases were produced from human cDNAs and purified by either GSH-affinity chromatography or immobilized metal. Affinity tags were removed from a number of kinases during purification. The purity of the protein kinases was examined by SDS-PAGE/Coomassie staining, the identity was checked by mass spectroscopy.

[00692] *Protein kinase assay:* A radiometric protein kinase assay (^{33}PanQinase® Activity Assay) was used for measuring the kinase activity of the three protein kinases. All kinase assays were performed in 96-well FlashPlates™ from PerkinElmer (Boston, MA, USA) in a 50 µl reaction volume. The reaction cocktail was pipetted in four steps in the following order:

- 20 µl of assay buffer (standard buffer)
- 5 µl of ATP solution (in H_2O)
- 5 µl of test compound (in 10 % DMSO)
- 20 µl enzyme/substrate mix

[00693] The assay for all protein kinases contained 70 mM HEPES-NaOH pH 7.5, 3 mM $MgCl_2$, 3 mM $MnCl_2$, 3 µM Na-orthovanadate, 1.2 mM DTT, 50 µg/ml PEG_{20000}, ATP (variable concentrations,

corresponding to the apparent ATP-K_m of the respective kinase), [γ-^{33}P]-ATP (approx. 9 x 10^{05}cpm per well), protein kinase (variable amounts), and substrate (variable amounts).

[00694] The following amounts of enzyme and substrate were used per well:

Kinase	*Kinase Conc.*	*Kinase Conc.*	*ATP Conc.*	*Substrate*	*Substrate*	*Substrate*
Name	*ng/50µl*	*nM **	*µM*	*Name*	*Lot*	*µg/50µl*
CDK12 wt/CycK	100	14.7	0.3	RBER-IRStide	036	2

* Maximal molar enzyme assay concentrations, implying enzyme preparations exclusively containing 100 % active enzyme

[00695] The reaction cocktails were incubated at 30°C for 60 minutes. The reaction was stopped with 50 µl of 2 % (v/v) H_3PO_4, plates were aspirated and washed two times with 200 µl 0.9 % (w/v) NaCl. Incorporation of ^{33}Pi was determined with a microplate scintillation counter (Microbeta, Wallac). All assays were performed with a BeckmanCoulter/SAGIAN™ Core System.

[00696] *Evaluation of raw data:* The median value of the counts in column 1 (n=8) of each assay plate was defined as "low control". This value reflects unspecific binding of radioactivity to the plate in the absence of a protein kinase but in the presence of the substrate. The median value of the counts in column 7 of each assay plate (n=8) was taken as the "high control", i.e. full activity in the absence of any inhibitor. The difference between high and low control was taken as 100 % activity.

[00697] As part of the data evaluation the low control value from a particular plate was subtracted from the high control value as well as from all 80 "compound values" of the corresponding plate. The residual activity (in %) for each well of a particular plate was calculated by using the following formula:

Res. Activity (%) = 100 X [(cpm of compound – low control) / (high control – low control)]

[00698] The residual activities for each concentration and the compound IC_{50} values were calculated using *Quattro Workflow V3.1.1* (Quattro Research GmbH, Munich, Germany). The fitting model for the IC_{50} determinations was "Sigmoidal response (variable slope)" with parameters "top" fixed at 100 % and "bottom" at 0 %. The fitting method used was a least-squares fit.

[00699] *Results:* The IC_{50} values for all compounds are compiled in Table 1. This table shows all IC_{50} values calculated, as well as the Hill slopes of the corresponding curves. All IC_{50} values that were out of range of the tested concentrations (< 3 x 10^{-09} M; > 1 x 10^{-04}M) are marked grey. A Hill slope higher than -0.4 is indicative that the curve is not sigmoidal, very flat or not descending.

Example 2 – Assay condition B (thiol-free conditions)

[00700] The IC_{50} profile of compounds was determined using one protein kinase in a customized, thiol free assay. IC_{50} values were measured by testing 10 concentrations (1×10^{-05} M to 3×10^{-10} M) of each test compound in singlicate against each kinase of interest. Prior to testing, the 1×10^{-03} M stock solutions in column 2 of the master plates were subjected to a serial, semi-logarithmic dilution using 100 % DMSO as a solvent. This resulted in 10 distinct concentrations, with a dilution endpoint of 3×10^{-08} M/100 % DMSO in column 12. Column 1 and 7 were filled with 100 % DMSO as controls. Subsequently, 2 x 10 microliter from each well of the serial diluted copy plates were aliquoted with a 96 channel pipettor into two identical sets of "compound dilution plates". All plates were barcoded for automated identification and tracking purposes. IC_{50} values were measured by testing 10 concentrations (1×10^{-05} M to 3×10^{-10} M) of each compound in singlicate. All compounds were stored as powder until being solubilized in DMSO. Solubilized compounds were stored as 1×10^{-02} M/100% DMSO stock solutions. Prior to the assay process, 90 microliters of H_2O were added to each well of a set of compound dilution plates. To minimize potential precipitation, the H_2O was added to each plate only a few minutes before the transfer of the compound solutions into the assay plates. Each plate was shaken thoroughly, resulting in compound dilution plates with a final of 10 % DMSO. For each assay, 5 microliters of solution from each well of the compound dilution plates/10 % DMSO were transferred into the assay plate. The final volume of the assay was 50 µl. All compounds were tested at 10 final assay concentrations in the range from 1×10^{-05} M to 3×10^{-10} M, in singlicate. The final DMSO concentration in the reaction cocktails was 1 % in all cases. A radiometric protein kinase assay (33PanQinase® Activity Assay) was used for measuring the kinase activity of the protein kinase. All kinase assays were performed in 96-well FlashPlatesTM from PerkinElmer (Boston, MA, USA) in a 50 microliter reaction volume. The reaction cocktail was pipetted in four steps in the following order: 20 microliter of assay buffer (standard buffer) • 5 microliter of ATP solution (in H_2O) • 5 microliter of test compound (in 10 % DMSO) • 20 microliter enzyme/subtrate mix. Each assay for the protein kinase contained 70 mM HEPES-NaOH pH 7.5, 3 mM $MgCl_2$, 3 mM $MnCl_2$, 3 microM Na-orthovanadate, 1 mM TCEP, 50 µg/ml PEG20000, ATP (corresponding to the apparent ATP-Km of the kinase, see Table A), [gamma-33P]-ATP (approx. 6 x 10xE5 cpm per well), with the protein kinase and relevant substrate being used in pre-determined amounts, depending on the kinase in question. For all experiments labeled as “Thiol-free”, all glutathione was exchanged from protein preparations so as to be removed from the assay and final buffer conditions contained no thiol- containing reagents. This was done so there would be no interference with the key cysteines in the proteins of interest.

[00701] For data analysis, the median value of the counts in column 1 (n=8) of each assay plate was defined as "low control". This value reflects unspecific binding of radioactivity to the plate in the absence of a protein kinase but in the presence of the substrate. The median value of the counts in column 7 of each assay plate (n=8) was taken as the "high control", i.e. full activity in the absence of any inhibitor. The difference between high and low control was taken as 100 % activity. As part of the data evaluation the low control value from a particular plate was subtracted from the high control value as well as from all 80 "compound values" of the corresponding plate. The residual activity (in %) for each well of a particular plate was calculated by using the following formula:

Res. Activity (%) = 100 X [(cpm of compound – low control) / (high control – low control)]

[00702] The residual activities for each concentration and the compound IC_{50} values were calculated using Quattro Workflow V3.1.1 (Quattro Research GmbH, Munich, Germany; www.quattro-research.com). The fitting model for the IC_{50} determinations was "Sigmoidal response (variable slope)" with parameters "top" fixed at 100 % and "bottom" at 0 %. The fitting method used was a least-squares fit. As a parameter for assay quality, the Z´-factor (Zhang et al., J. Biomol. Screen. 2: 67-73, 1999) for the low and high controls of each assay plate (n = 8) was used. ProQinase´s criterion for repetition of an assay plate is a Z´-factor below 0.4 (Iversen et al., J. Biomol. Screen. 3: 247-252, 2006).

[00703] Representative data for exemplary compounds disclosed herein are presented in the following Table 6.

Table 6

Synthetic Chemistry Example	CDK12 IC_{50} Condition A	CDk12 IC_{50} Condition B
1	---	A
2	---	B
3	---	A
4	---	B
5	---	A
6	---	A
7	---	A
8	---	B
9	---	A
10	---	A

Synthetic Chemistry Example	CDK12 IC_{50} Condition A	CDk12 IC_{50} Condition B
11	---	A
12	---	B
13	---	C
14	A	A
15	---	B
16	---	C
17	B	B
18	---	B
19	A	A
20	A	A
21	---	A
22	---	B
23	---	B
24	---	A
25	A	A
26	A	A
27	---	A
28	B	B
29	B	A
30	---	A
31	---	A
32	---	B
33	---	C
34	---	B
35	---	E
36	---	E
37	---	C
38	---	D
39	---	E
40	---	D
41	---	E
42	---	E

Synthetic Chemistry Example	CDK12 IC_{50} Condition A	CDk12 IC_{50} Condition B
43	---	C
44	---	B
45	---	B
46	---	C
47	A	A
48	---	B
49	---	A
50	---	A
51	---	B
52	B	A
53	B	B
54	A	A
55	B	A
56	---	A
57	---	B
58	B	A
59	C	B
60	---	B
61	---	C
62	A	A
63	---	B
64	---	B
65	---	A
66	---	A
67	---	A
68	---	A
69	---	B
70	B	---
71	---	B
72	---	A
73	---	B
74	---	A

Synthetic Chemistry Example	CDK12 IC_{50} Condition A	CDk12 IC_{50} Condition B
75	---	C
76	---	A
77	B	---
78	---	A
79	---	A
80	---	B
81	---	B
82	---	B
83	---	B
84	---	B
85	---	B
86	A	---
87	B	---
88	A	---
89	B	---
90	A	---
91	A	---
92	A	---
93	A	---
94	B	---
95	A	---
96	A	---
97	E	---
98	C	---
99	B	---
100	B	---
101	B	---
102	A	---
103	B	---
104	A	---
105	B	---
106	D	---

Synthetic Chemistry Example	CDK12 IC_{50} Condition A	CDk12 IC_{50} Condition B
107	C	---
108	E	---
109	D	---
110	C	---
111	A	---
112	B	---
113	---	B
114	B	---
115	B	---
116	C	---
117	B	---
118	D	---
119	B	---
120	A	---
121	C	---
122	D	---
123	B	---
124	A	---
125	A	---
126	B	---
127	B	---
128	C	---
129	B	---
130	B	---
131	B	---
132	C	---
133	B	---
134	B	---
135	C	---
136	B	---
137	A	---
138	A	---

Synthetic Chemistry Example	CDK12 IC_{50} Condition A	CDk12 IC_{50} Condition B
139	A	---
140	C	---
141	C	---
142	C	---
143	A	---
144	A	---
145	B	---
146	C	---
147	B	---
148	B	---
149	C	---
150	B	---
151	A	---
152	A	---
153	B	---
154	A	---
155	D	---
156	B	---
157	A	---
158	B	---
159	C	---
160	D	---
161	---	---
162	B	---
163	A	---
164	A	---
165	A	---
166	B	---
167	A	---
168	B	---
169	A	---
170	B	---

Synthetic Chemistry Example	CDK12 IC_{50} Condition A	CDk12 IC_{50} Condition B
171	B	---
172	B	---
173	B	---
174	B	---
175	B	---
176	B	---
177	B	---
178	B	---
179	B	---
180	A	---
181	A	---
182	A	---
183	A	---
184	A	---

Note: Biochemical assay IC_{50} data are designated within the following ranges:
A: ≤ 0.10 μM C: > 1.0 μM to ≤ 10 μM E: >30 μM to ≤ 100 μM
B: > 0.10 μM to ≤ 1.0 μM D: > 10 μM to ≤ 30 μM

III. Preparation of Pharmaceutical Dosage Forms

Example 1: Oral capsule

[00704] The active ingredient is a compound of Table 1, or a pharmaceutically acceptable salt thereof. A capsule for oral administration is prepared by mixing 1-1000 mg of active ingredient with starch or other suitable powder blend. The mixture is incorporated into an oral dosage unit such as a hard gelatin capsule, which is suitable for oral administration.

Example 2: Solution for injection

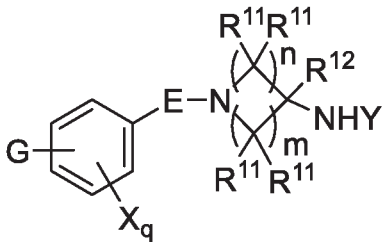
[00705] The active ingredient is a compound of Table 1, or a pharmaceutically acceptable salt thereof, and is formulated as a solution in sesame oil at a concentration of 50 mg-eq/mL.

[00706] 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

We claim:

1. A compound, or pharmaceutically acceptable salt or solvate thereof, having the structure of Formula (I):

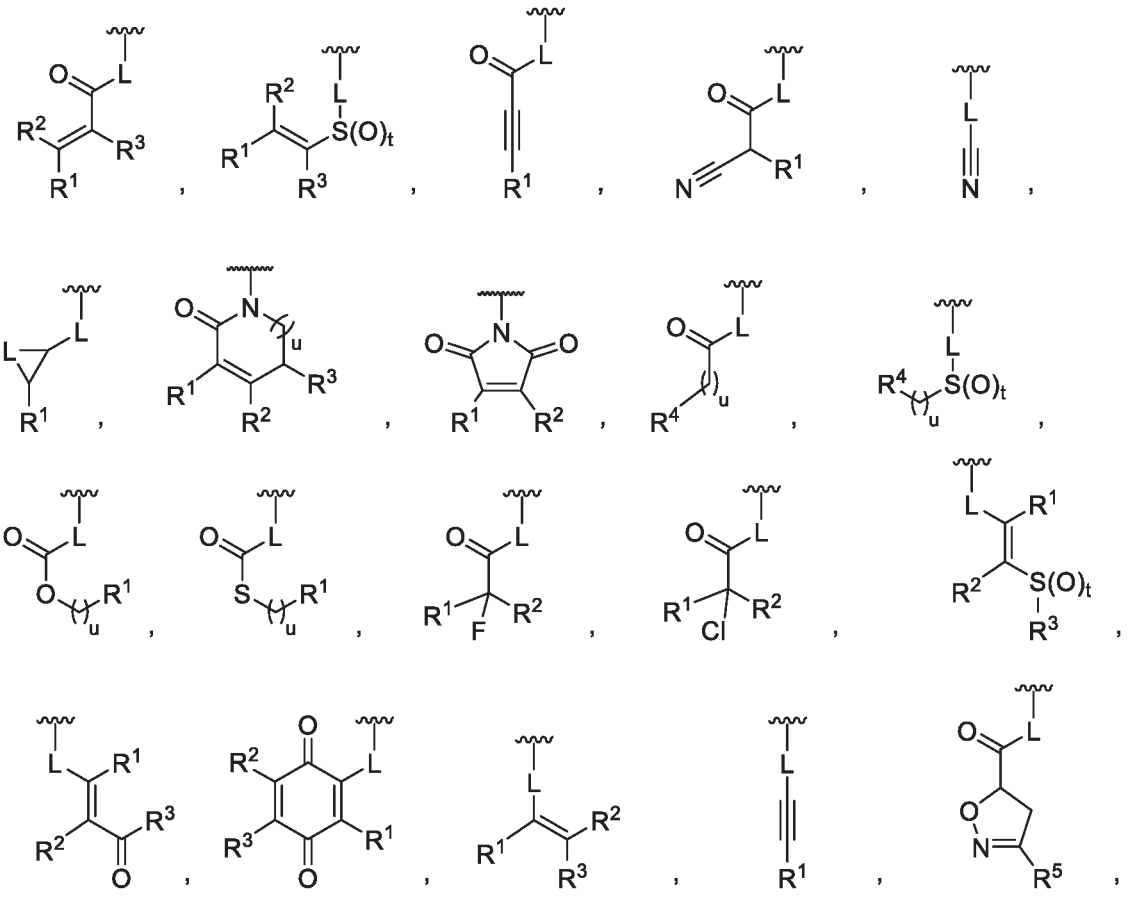


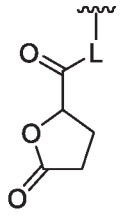
(I)

wherein,

E is selected from a bond, $-SO_2-$, $-C(O)-$, $-CH_2-$, $-CH(R^4)-$, or $-C(R^4)_2-$;

G is selected from a group having the structure:

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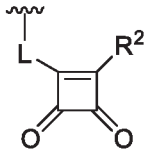
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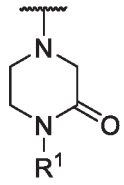
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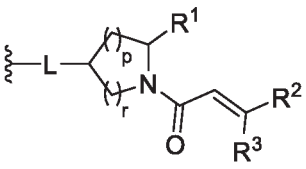
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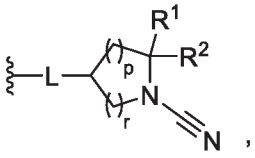
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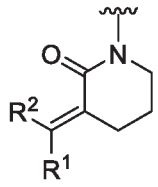
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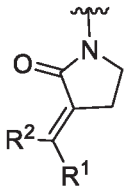

;

wherein,

L is O, NH, N(optionally substituted C1-C4 alkyl), or -NH-CH_2-* wherein the * denotes the point of attachment to the phenyl ring;

t is 0, 1, or 2;

u is 1, or 2;

p is 0, 1, or 2;

r is 0, 1, or 2;

R^1 is selected from hydrogen, optionally substituted C1-C4 alkyl, or optionally substituted heterocyclylalkyl;

R^2 is selected from hydrogen, or optionally substituted C1-C4 alkyl;

R^3 is selected from hydrogen, -CN, or optionally substituted C1-C4 alkyl;

each R^4 is independently selected from optionally substituted C1-C4 alkyl, or optionally substituted heterocyclylalkyl;

R^5 is optionally substituted C1-C4 alkyl, or optionally substituted heterocyclylalkyl;

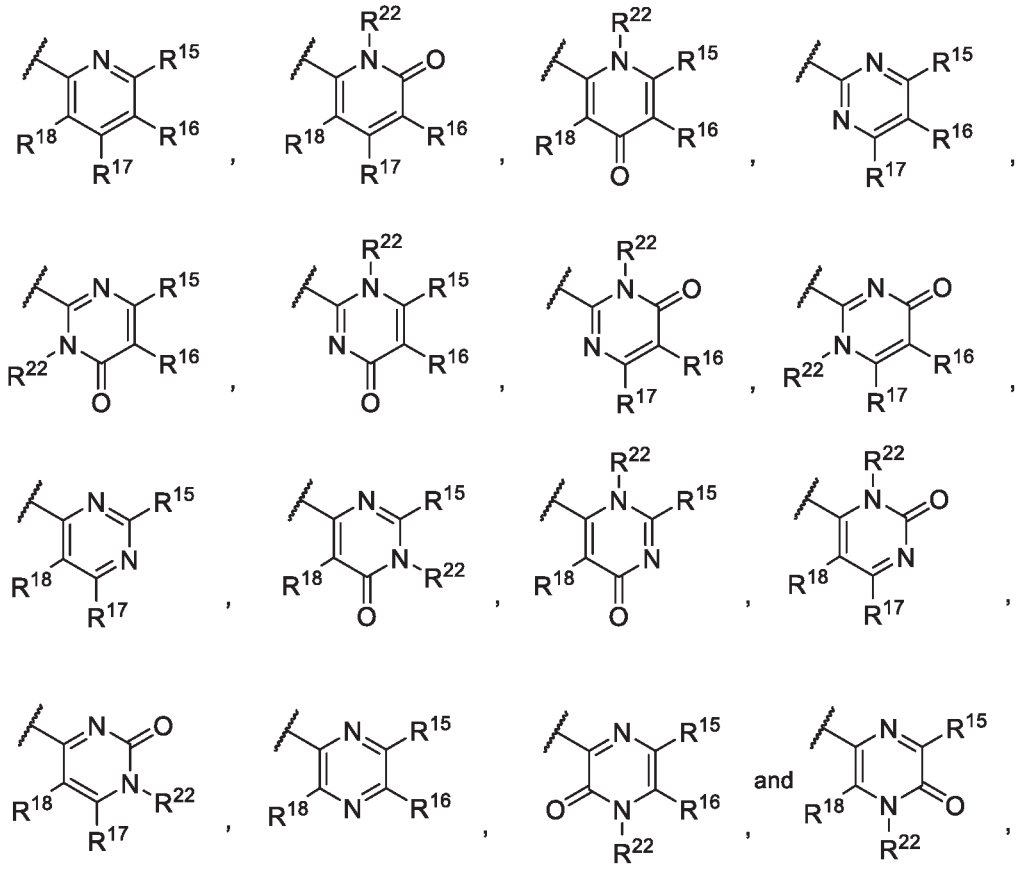
each R^{11} is independently hydrogen, halogen, optionally substituted C1-C6 alkyl, -OH, optionally substituted C1-C4 alkoxy, or two R^{11} groups on the same carbon atom form an oxo;

R^{12} is hydrogen or optionally substituted C1-C4 alkyl;

q is 0, 1, 2, or 3; n is 0, 1, 2, or 3; m is 0, 1, 2, or 3;

each X is independently halogen, optionally substituted C1-C4 alkyl, optionally substituted C1-C4 alkoxy, optionally substituted aminoalkyl, optionally substituted cycloalkyl, optionally substituted heterocyclyl, optionally substituted aryl, or optionally substituted heteroaryl;

Y is a group selected from:



wherein,

R^{15} is selected from hydrogen, halogen, -CN, optionally substituted alkyl, optionally substituted fluoroalkyl, optionally substituted alkoxy, optionally substituted cycloalkyl, optionally substituted heterocyclyl, optionally substituted cycloalkylalkyl, optionally substituted cycloalkyl-O-, optionally substituted aryl, optionally substituted aralkyl, optionally substituted aryloxy, optionally substituted aralkyloxy, optionally substituted heteroaryloxy, optionally substituted heteroaralkyloxy, $-OR^{22}$, $-N(R^{22})_2$, $-SO_2R^{21}$, $-N(R^{22})SO_2R^{21}$, $-SO_2N(R^{22})_2$, $-N(R^{22})SO_2N(R^{22})_2$, $-CON(R^{22})_2$, $-N(R^{22})CO_2R^{21}$, $-N(R^{22})CON(R^{22})_2$, $-N(R^{22})COR^{21}$, $-OC(O)N(R^{22})_2$, $-OSO_2N(R^{22})_2$, or $-N(R^{22})SO_3R^{21}$;

R^{16} is selected from hydrogen, halogen, -CN, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted fluoroalkyl, optionally substituted alkoxy, optionally substituted cycloalkyl, optionally substituted heterocyclyl, optionally substituted cycloalkylalkyl, optionally substituted cycloalkyl-O-, optionally substituted aryl, optionally substituted aralkyl, optionally substituted heteroaryl, optionally substituted heteroaralkyl, optionally substituted aryloxy, optionally substituted aralkyloxy, optionally substituted heteroaryloxy, optionally substituted heteroaralkyloxy, $-OR^{22}$, $-N(R^{22})_2$, $-SO_2R^{21}$, $-N(R^{22})SO_2R^{21}$, $-SO_2N(R^{22})_2$, $-N(R^{22})SO_2N(R^{22})_2$, $-CON(R^{22})_2$, $-N(R^{22})CO_2R^{21}$, $-N(R^{22})CON(R^{22})_2$, $-N(R^{22})COR^{21}$, $-OC(O)N(R^{22})_2$, $-OSO_2N(R^{22})_2$, or $-N(R^{22})SO_3R^{21}$;

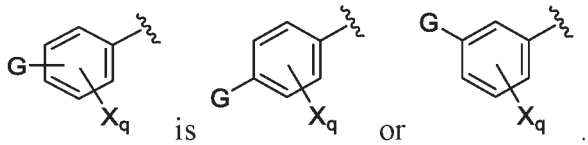
R^{17} is selected from hydrogen, halogen, -CN, optionally substituted alkyl, optionally substituted fluoroalkyl, optionally substituted alkoxy, optionally substituted cycloalkyl, optionally substituted heterocyclyl, optionally substituted cycloalkylalkyl, optionally substituted cycloalkyl-O-, optionally substituted aryl, optionally substituted aralkyl, optionally substituted aryloxy, optionally substituted aralkyloxy, optionally substituted heteroaryloxy, optionally substituted heteroaralkyloxy, $-OR^{22}$, $-N(R^{22})_2$, $-SO_2R^{21}$, $-N(R^{22})SO_2R^{21}$, $-SO_2N(R^{22})_2$, $-N(R^{22})SO_2N(R^{22})_2$, $-CON(R^{22})_2$, $-N(R^{22})CO_2R^{21}$, $-N(R^{22})CON(R^{22})_2$, $-N(R^{22})COR^{21}$, $-OC(O)N(R^{22})_2$, $-OSO_2N(R^{22})_2$, or $-N(R^{22})SO_3R^{21}$;

R^{18} is selected from hydrogen, halogen, -CN, optionally substituted alkyl, optionally substituted fluoroalkyl, optionally substituted alkoxy, optionally substituted cycloalkyl, optionally substituted heterocyclyl, optionally substituted cycloalkylalkyl, optionally substituted cycloalkyl-O-, optionally substituted aryl, optionally substituted aralkyl, optionally substituted heteroaryl, optionally substituted heteroaralkyl, optionally substituted aryloxy, optionally substituted aralkyloxy, optionally substituted heteroaryloxy, optionally substituted heteroaralkyloxy, $-OR^{22}$, $-N(R^{22})_2$, $-SO_2R^{21}$, $-N(R^{22})SO_2R^{21}$, $-SO_2N(R^{22})_2$, $-N(R^{22})SO_2N(R^{22})_2$, $-CON(R^{22})_2$, $-N(R^{22})CO_2R^{21}$, $-N(R^{22})CON(R^{22})_2$, $-N(R^{22})COR^{21}$, $-OC(O)N(R^{22})_2$, $-OSO_2N(R^{22})_2$, or $-N(R^{22})SO_3R^{21}$;

each R^{21} is independently selected from alkyl, cycloalkyl, cycloalkylalkyl, aryl, aralkyl, heterocyclyl, heterocyclylalkyl, heteroaryl, or heteroarylalkyl; and

each R^{22} is independently selected from hydrogen, alkyl, cycloalkyl, cycloalkylalkyl, aryl, aralkyl, heterocyclyl, heterocyclylalkyl, heteroaryl, or heteroarylalkyl.

2. The compound of claim 1, or pharmaceutically acceptable salt or solvate thereof, wherein



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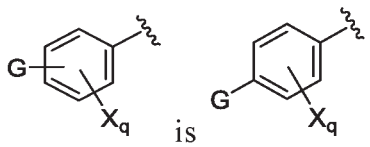
3. The compound of claim 1 or 2, or pharmaceutically acceptable salt or solvate thereof, wherein



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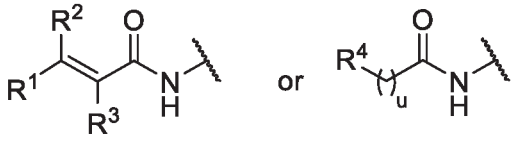
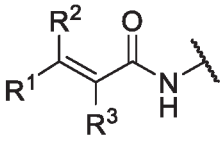
4. The compound of any one of claims 1-3, or pharmaceutically acceptable salt or solvate thereof, wherein G is  .

5. The compound of claim 4, or pharmaceutically acceptable salt or solvate thereof, wherein G is  .

6. The compound of claim 5 or pharmaceutically acceptable salt or solvate thereof, wherein R^3 is hydrogen or –CN.

7. The compound of claim 1, or pharmaceutically acceptable salt or solvate thereof, wherein L is NH.

8. The compound of claim 1, or pharmaceutically acceptable salt or solvate thereof, wherein t is 2.

9. The compound of claim 1, or pharmaceutically acceptable salt or solvate thereof, wherein q is 0, 1, or 2.

10. The compound of claim 1, or pharmaceutically acceptable salt or solvate thereof, wherein q is 0, or 1.

11. The compound of any one of claims 1-10, or pharmaceutically acceptable salt or solvate thereof, wherein X is a halogen.

12. The compound of any one of claims 1-11, or pharmaceutically acceptable salt or solvate thereof, wherein R^2 is hydrogen.

13. The compound of any one of claims 1-12, or pharmaceutically acceptable salt or solvate thereof, wherein R^3 is hydrogen.

14. The compound of any one of claims 1-13, or pharmaceutically acceptable salt or solvate thereof, wherein R^2 and R^3 is hydrogen.

15. The compound of any one of claims 1-14, or pharmaceutically acceptable salt or solvate thereof, wherein R^1 is hydrogen.

16. The compound of any one of claims 1-14, or pharmaceutically acceptable salt or solvate thereof, wherein R^1 is optionally substituted C1-C4 alkyl.

17. The compound of any one of claims 1-14, or pharmaceutically acceptable salt or solvate thereof, wherein R^1 is optionally substituted C1-C2 alkyl.

18. The compound of any one of claims 1-14, or pharmaceutically acceptable salt or solvate thereof, wherein R^1 is optionally substituted C1 alkyl.

19. The compound of claim 18, or pharmaceutically acceptable salt or solvate thereof, wherein the C1 alkyl is substituted with an optionally substituted amino group.

20. The compound of claim 19, or pharmaceutically acceptable salt or solvate thereof, wherein the optionally substituted amino group is a dimethylamino.

21. The compound of any one of claims 1-14, or pharmaceutically acceptable salt or solvate thereof, wherein R^1 is $–CH_2\text{-}N(Me)_2$.

22. The compound of any one of claims 1-14, or pharmaceutically acceptable salt or solvate thereof, wherein R^1 is optionally substituted heterocyclylalkyl.

23. The compound of claim 22, or pharmaceutically acceptable salt or solvate thereof, wherein the optionally substituted heterocyclylalkyl comprises an optionally substituted C1 alkyl.

24. The compound of claim 22 or 23, or pharmaceutically acceptable salt or solvate thereof, wherein the optionally substituted heterocyclylalkyl comprises an optionally substituted N-linked heterocyclyl.

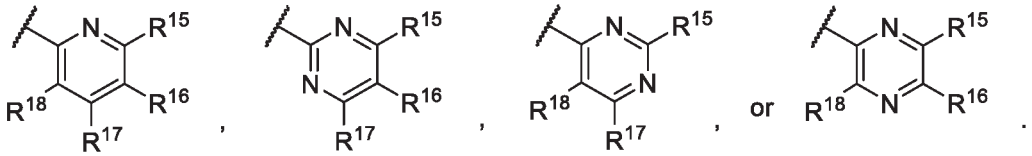
25. The compound of claim 24, or pharmaceutically acceptable salt or solvate thereof, wherein the optionally substituted N-linked heterocyclyl is an N-linked pyrrolidine or piperidine.

26. The compound of any one of claims 1-25, or pharmaceutically acceptable salt or solvate thereof, wherein n is 1 and m is 1.

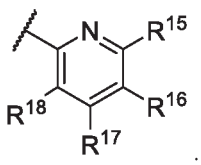
27. The compound of any one of claims 1-25, or pharmaceutically acceptable salt or solvate thereof, wherein n is 1 and m is 2.

28. The compound of any one of claims 1-25, or pharmaceutically acceptable salt or solvate thereof, wherein n is 1 and m is 3.

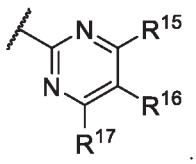
29. The compound of any one of claims 1-28, or pharmaceutically acceptable salt or solvate thereof, wherein Y is selected from:



30. The compound of any one of claims 1-28, or pharmaceutically acceptable salt or solvate thereof, wherein Y is:



31. The compound of any one of claims 1-28, or pharmaceutically acceptable salt or solvate thereof, wherein Y is:



32. The compound of any one of claims 29-31, or pharmaceutically acceptable salt or solvate thereof, wherein R^{15} is hydrogen.

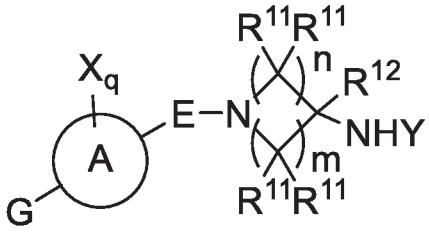
33. The compound of any one of claims 29-31, or pharmaceutically acceptable salt or solvate thereof, wherein R^{16} is hydrogen.

34. The compound of any one of claims 29-31, or pharmaceutically acceptable salt or solvate thereof, wherein R^{17} is hydrogen.

35. The compound of any one of claims 29-31, or pharmaceutically acceptable salt or solvate thereof, wherein R^{18} is hydrogen.

36. The compound of any one of claims 29-31, or pharmaceutically acceptable salt or solvate thereof, wherein R^{15} and R^{16} are hydrogen.

37. A compound, or pharmaceutically acceptable salt or solvate thereof, having the structure of Formula (II):



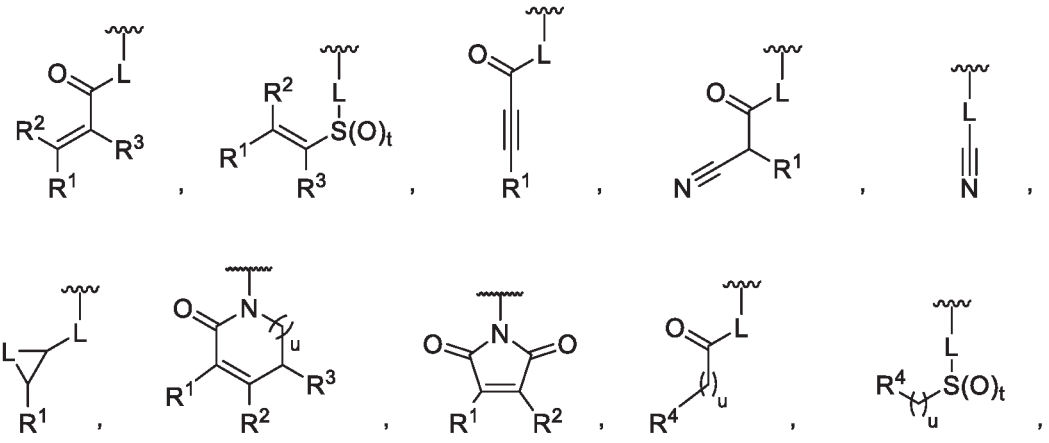
(II)

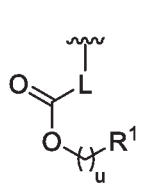
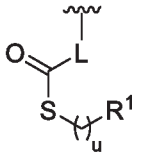
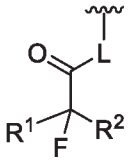
wherein,

ring A is a monocyclic heteroaryl;

E is selected from a bond, $-SO_2-$, $-C(O)-$, $-CH_2-$, $-CH(R^4)-$, or $-C(R^4)_2-$;

G is selected from a group having the structure:

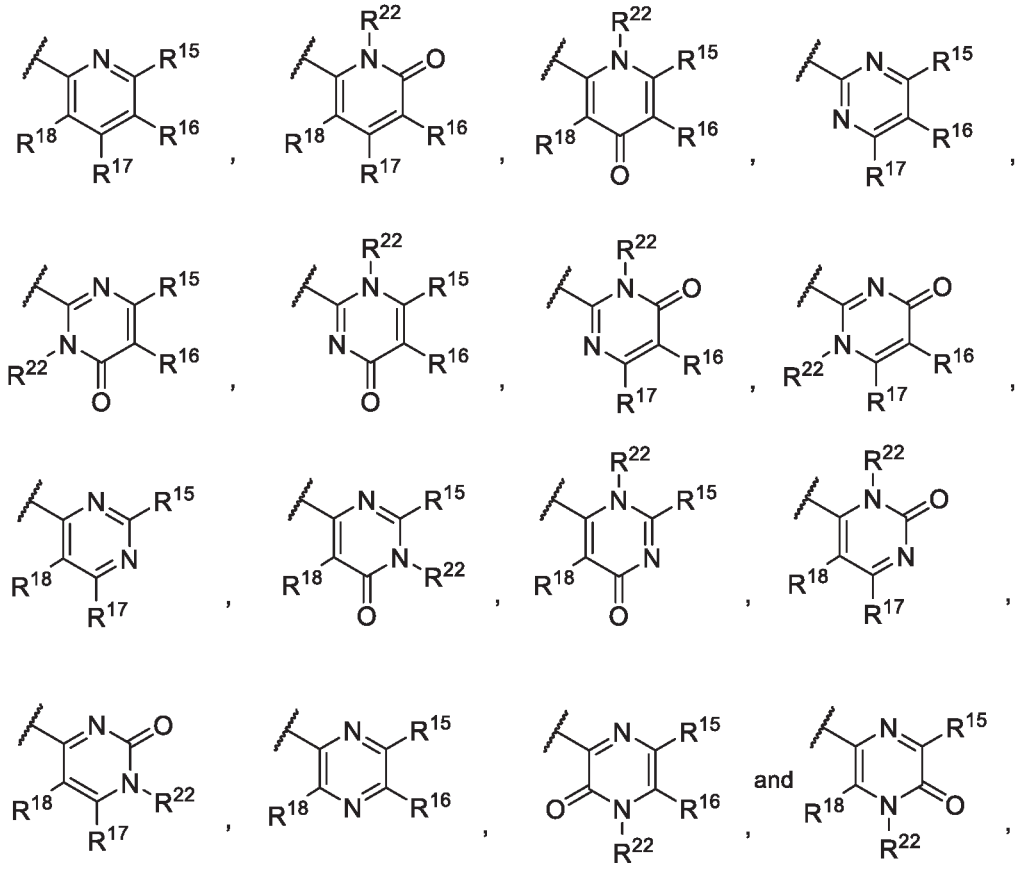


n is 0, 1, 2, or 3; m is 0, 1, 2, or 3;

each X is independently halogen, optionally substituted C1-C4 alkyl, optionally substituted C1-C4 alkoxy, optionally substituted aminoalkyl, optionally substituted cycloalkyl, optionally substituted heterocyclyl, optionally substituted aryl, or optionally substituted heteroaryl;

Y is a group selected from:



wherein,

R^{15} is selected from hydrogen, halogen, -CN, optionally substituted alkyl, optionally substituted fluoroalkyl, optionally substituted alkoxy, optionally substituted cycloalkyl, optionally substituted heterocyclyl, optionally substituted cycloalkylalkyl, optionally substituted cycloalkyl-O-, optionally substituted aryl, optionally substituted aralkyl, optionally substituted heteroaryl, optionally substituted heteroaralkyl, optionally substituted aryloxy, optionally substituted aralkyloxy, optionally substituted heteroaryloxy, optionally substituted heteroaralkyloxy, $-OR^{22}$, $-N(R^{22})_2$, $-SO_2R^{21}$, $-N(R^{22})SO_2R^{21}$, $-SO_2N(R^{22})_2$, $-N(R^{22})SO_2N(R^{22})_2$, $-CON(R^{22})_2$, $-N(R^{22})CO_2R^{21}$, $-N(R^{22})CON(R^{22})_2$, $-N(R^{22})COR^{21}$, $-OC(O)N(R^{22})_2$, $-OSO_2N(R^{22})_2$, or $-N(R^{22})SO_3R^{21}$;

R^{16} is selected from hydrogen, halogen, -CN, optionally substituted alkyl, optionally substituted fluoroalkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted alkoxy, optionally substituted cycloalkyl, optionally substituted heterocyclyl, optionally

substituted cycloalkylalkyl, optionally substituted cycloalkyl-O-, optionally substituted aryl, optionally substituted aralkyl, optionally substituted heteroaryl, optionally substituted heteroaralkyl, optionally substituted aryloxy, optionally substituted aralkyloxy, optionally substituted heteroaryloxy, optionally substituted heteroaralkyloxy, $-OR^{22}$, $-N(R^{22})_2$, $-SO_2R^{21}$, $-N(R^{22})SO_2R^{21}$, $-SO_2N(R^{22})_2$, $-N(R^{22})SO_2N(R^{22})_2$, $-CON(R^{22})_2$, $-N(R^{22})CO_2R^{21}$, $-N(R^{22})CON(R^{22})_2$, $-N(R^{22})COR^{21}$, $-OC(O)N(R^{22})_2$, $-OSO_2N(R^{22})_2$, or $-N(R^{22})SO_3R^{21}$;

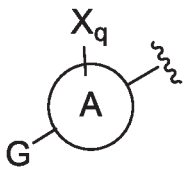
R^{17} is selected from hydrogen, halogen, -CN, optionally substituted alkyl, optionally substituted fluoroalkyl, optionally substituted alkoxy, optionally substituted cycloalkyl, optionally substituted heterocyclyl, optionally substituted cycloalkylalkyl, optionally substituted cycloalkyl-O-, optionally substituted aryl, optionally substituted aralkyl, optionally substituted heteroaryl, optionally substituted heteroaralkyl, optionally substituted aryloxy, optionally substituted aralkyloxy, optionally substituted heteroaryloxy, optionally substituted heteroaralkyloxy, $-OR^{22}$, $-N(R^{22})_2$, $-SO_2R^{21}$, $-N(R^{22})SO_2R^{21}$, $-SO_2N(R^{22})_2$, $-N(R^{22})SO_2N(R^{22})_2$, $-CON(R^{22})_2$, $-N(R^{22})CO_2R^{21}$, $-N(R^{22})CON(R^{22})_2$, $-N(R^{22})COR^{21}$, $-OC(O)N(R^{22})_2$, $-OSO_2N(R^{22})_2$, or $-N(R^{22})SO_3R^{21}$;

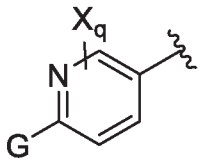
R^{18} is selected from hydrogen, halogen, -CN, optionally substituted alkyl, optionally substituted fluoroalkyl, optionally substituted alkoxy, optionally substituted cycloalkyl, optionally substituted heterocyclyl, optionally substituted cycloalkylalkyl, optionally substituted cycloalkyl-O-, optionally substituted aryl, optionally substituted aralkyl, optionally substituted heteroaryl, optionally substituted heteroaralkyl, optionally substituted aryloxy, optionally substituted aralkyloxy, optionally substituted heteroaryloxy, optionally substituted heteroaralkyloxy, $-OR^{22}$, $-N(R^{22})_2$, $-SO_2R^{21}$, $-N(R^{22})SO_2R^{21}$, $-SO_2N(R^{22})_2$, $-N(R^{22})SO_2N(R^{22})_2$, $-CON(R^{22})_2$, $-N(R^{22})CO_2R^{21}$, $-N(R^{22})CON(R^{22})_2$, $-N(R^{22})COR^{21}$, $-OC(O)N(R^{22})_2$, $-OSO_2N(R^{22})_2$, or $-N(R^{22})SO_3R^{21}$;

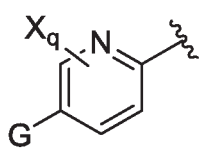
each R^{21} is independently selected from alkyl, cycloalkyl, cycloalkylalkyl, aryl, aralkyl, heterocyclyl, heterocyclylalkyl, heteroaryl, or heteroarylalkyl; and

each R^{22} is independently selected from hydrogen, alkyl, cycloalkyl, cycloalkylalkyl, aryl, aralkyl, heterocyclyl, heterocyclylalkyl, heteroaryl, or heteroarylalkyl.

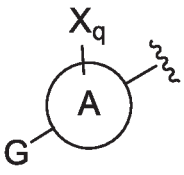
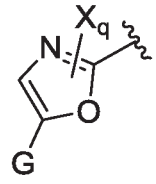
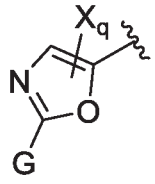
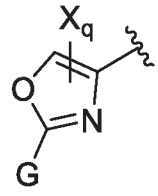
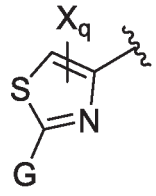
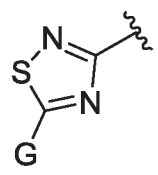
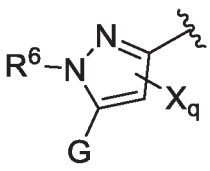
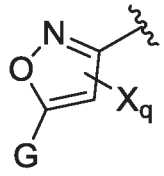
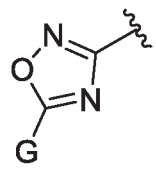
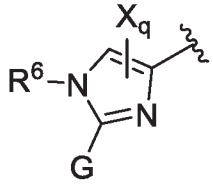
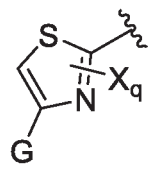
38. The compound of claim 37, or pharmaceutically acceptable salt or solvate thereof, wherein

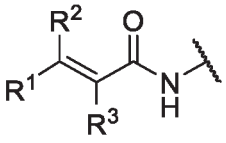
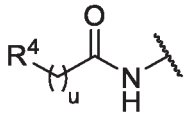


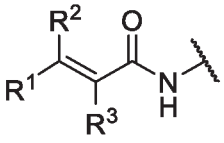
is


or


; and q is 0, 1, 2, or 3.

39. The compound of claim 37, or pharmaceutically acceptable salt or solvate thereof, wherein  is , , , , , , , , , or ; R^6 is hydrogen or optionally substituted C1-C4 alkyl; and q is 0 or 1.

40. The compound of any one of claims 37-39, or pharmaceutically acceptable salt or solvate thereof, wherein G is  or .

41. The compound of any one of claims 37-40, or pharmaceutically acceptable salt or solvate thereof, wherein G is .

42. The compound of claim 41 or pharmaceutically acceptable salt or solvate thereof, wherein R^3 is hydrogen or –CN.

43. The compound of claim 37, or pharmaceutically acceptable salt or solvate thereof, wherein L is NH.

44. The compound of claim 37, or pharmaceutically acceptable salt or solvate thereof, wherein t is 2.

45. The compound of claim 37, or pharmaceutically acceptable salt or solvate thereof, wherein q is 0 or 1.

46. The compound of claim 37, or pharmaceutically acceptable salt or solvate thereof, wherein q is 0.

47. The compound of any one of claims 37-46, or pharmaceutically acceptable salt or solvate thereof, wherein X is a halogen.

48. The compound of any one of claims 37-47, or pharmaceutically acceptable salt or solvate thereof, wherein R^2 is hydrogen.

49. The compound of any one of claims 37-47, or pharmaceutically acceptable salt or solvate thereof, wherein R^3 is hydrogen.

50. The compound of any one of claims 37-47, or pharmaceutically acceptable salt or solvate thereof, wherein R^2 and R^3 is hydrogen.

51. The compound of any one of claims 37-50, or pharmaceutically acceptable salt or solvate thereof, wherein R^1 is hydrogen.

52. The compound of any one of claims 37-50, or pharmaceutically acceptable salt or solvate thereof, wherein R^1 is optionally substituted C1-C4 alkyl.

53. The compound of any one of claims 37-50, or pharmaceutically acceptable salt or solvate thereof, wherein R^1 is optionally substituted C1-C2 alkyl.

54. The compound of any one of claims 37-50, or pharmaceutically acceptable salt or solvate thereof, wherein R^1 is optionally substituted C1 alkyl.

55. The compound of claim 54, or pharmaceutically acceptable salt or solvate thereof, wherein the C1 alkyl is substituted with an optionally substituted amino group.

56. The compound of claim 55, or pharmaceutically acceptable salt or solvate thereof, wherein the optionally substituted amino group is a dimethylamino.

57. The compound of any one of claims 37-56, or pharmaceutically acceptable salt or solvate thereof, wherein R^1 is $–CH_2\text{-}N(Me)_2$.

58. The compound of any one of claims 37-54, or pharmaceutically acceptable salt or solvate thereof, wherein R^1 is optionally substituted heterocyclylalkyl.

59. The compound of claim 58, or pharmaceutically acceptable salt or solvate thereof, wherein the optionally substituted heterocyclylalkyl comprises an optionally substituted C1 alkyl.

60. The compound of claim 58 or 59, or pharmaceutically acceptable salt or solvate thereof, wherein the optionally substituted heterocyclylalkyl comprises an optionally substituted N-linked heterocyclyl.

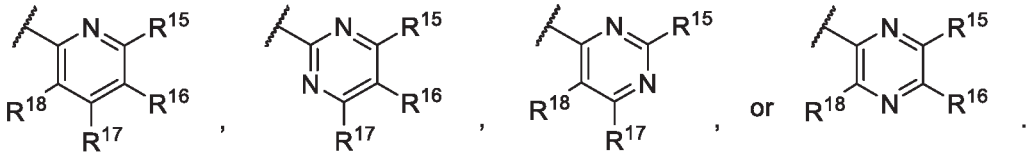
61. The compound of claim 60, or pharmaceutically acceptable salt or solvate thereof, wherein the optionally substituted N-linked heterocyclyl is an N-linked pyrrolidine or piperidine.

62. The compound of any one of claims 37-61, or pharmaceutically acceptable salt or solvate thereof, wherein n is 1 and m is 1.

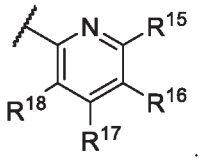
63. The compound of any one of claims 37-61, or pharmaceutically acceptable salt or solvate thereof, wherein n is 1 and m is 2.

64. The compound of any one of claims 37-61, or pharmaceutically acceptable salt or solvate thereof, wherein n is 1 and m is 3.

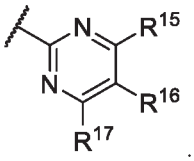
65. The compound of any one of claims 37-64, or pharmaceutically acceptable salt or solvate thereof, wherein Y is selected from:



66. The compound of any one of claims 37-64, or pharmaceutically acceptable salt or solvate thereof, wherein Y is:



67. The compound of any one of claims 37-64, or pharmaceutically acceptable salt or solvate thereof, wherein Y is:



68. The compound of any one of claims 65-67, or pharmaceutically acceptable salt or solvate thereof, wherein R^{15} is hydrogen.

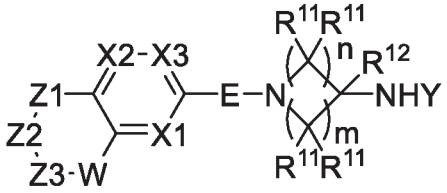
69. The compound of any one of claims 65-67, or pharmaceutically acceptable salt or solvate thereof, wherein R^{16} is hydrogen.

70. The compound of any one of claims 65-67, or pharmaceutically acceptable salt or solvate thereof, wherein R^{17} is hydrogen.

71. The compound of any one of claims 65-67, or pharmaceutically acceptable salt or solvate thereof, wherein R^{18} is hydrogen.

72. The compound of any one of claims 65-67, or pharmaceutically acceptable salt or solvate thereof, wherein R^{15} and R^{16} are hydrogen.

73. A compound, or pharmaceutically acceptable salt or solvate thereof, having the structure of Formula (III):



(III)

wherein,

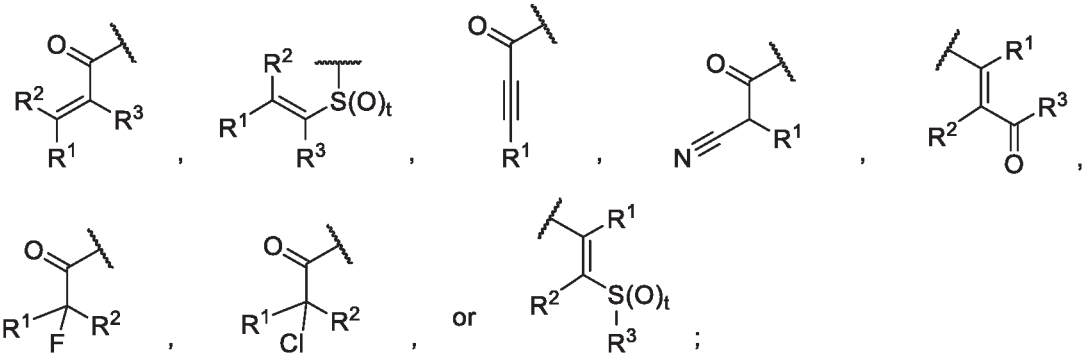
Z1, Z2, and Z3 are selected from CH_2 or N-G, with the provision that only one of Z1, Z2, or Z3 is N-G;

X1, X2 and X3 are each independently N or C-R^7;

W is absent, O, S, SO_2, NH, NR^{12}, $C(R^{11})_2$;

E is selected from a bond, -SO_2-, -C(O)-, –CH_2-, -$CH(R^4)$-, or -$C(R^4)_2$-;

G is selected from a group having the structure:



wherein,

t is 0, 1, or 2;

R^1 is selected from hydrogen, optionally substituted C1-C4 alkyl, or optionally substituted heterocyclylalkyl;

R^2 is selected from hydrogen, or optionally substituted C1-C4 alkyl;

R^3 is selected from hydrogen, -CN, or optionally substituted C1-C4 alkyl;

each R^4 is independently selected from optionally substituted C1-C4 alkyl, or optionally substituted heterocyclylalkyl;

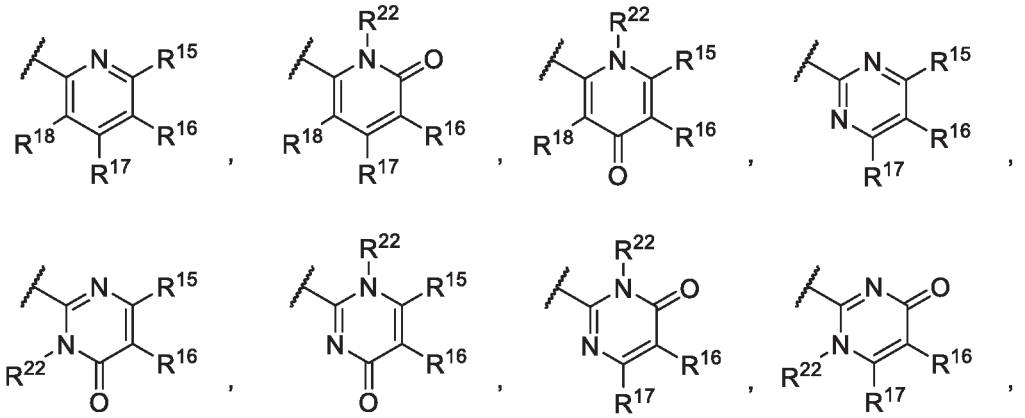
each R^7 is independently hydrogen, halogen, optionally substituted C1-C4 alkyl, optionally substituted C1-C4 alkoxy, optionally substituted cycloalkyl, optionally substituted heterocyclyl, optionally substituted aryl, or optionally substituted heteroaryl

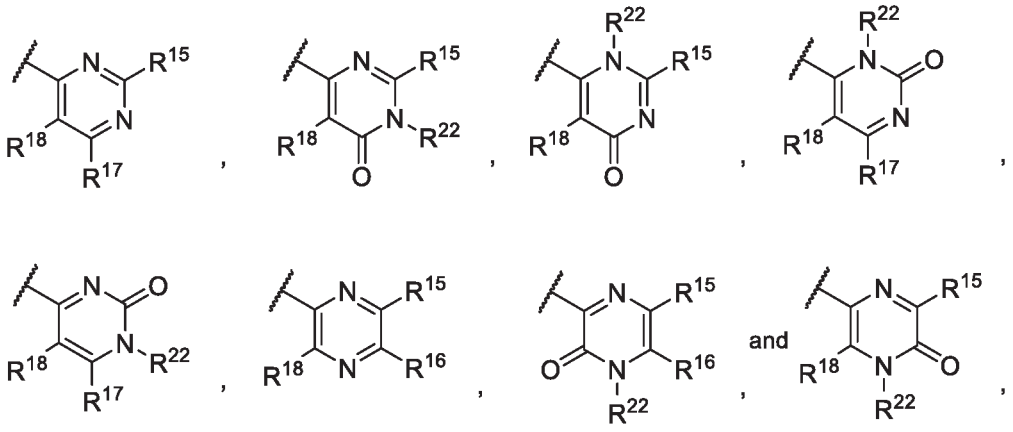
each R^{11} is independently hydrogen, halogen, optionally substituted C1-C6 alkyl, or two R^{11} groups on the same carbon atom form an oxo;

each R^{12} is independently hydrogen or optionally substituted C1-C4 alkyl;

n is 0, 1, 2, or 3; m is 0, 1, 2, or 3;

Y is a group selected from:





wherein,

R^{15} is selected from hydrogen, halogen, -CN, optionally substituted alkyl, optionally substituted alkoxy, optionally substituted cycloalkyl, optionally substituted heterocyclyl, optionally substituted cycloalkylalkyl, optionally substituted cycloalkyl-O-, optionally substituted aryl, optionally substituted aralkyl, optionally substituted heteroaryl, optionally substituted heteroaralkyl, optionally substituted aryloxy, optionally substituted aralkyloxy, optionally substituted heteroaryloxy, optionally substituted heteroaralkyloxy, $-N(R^{22})_2$, $-SO_2R^{21}$, $-N(R^{22})SO_2R^{21}$, $-SO_2N(R^{22})_2$, $-N(R^{22})SO_2N(R^{22})_2$, $-CON(R^{22})_2$, $-N(R^{22})CO_2R^{21}$, $-N(R^{22})CON(R^{22})_2$, $-N(R^{22})COR^{21}$, $-OC(O)N(R^{22})_2$, $-OSO_2N(R^{22})_2$, or $-N(R^{22})SO_3R^{21}$;

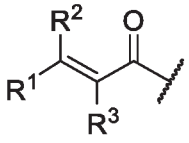
R^{16} is selected from hydrogen, halogen, -CN, optionally substituted alkyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted alkoxy, optionally substituted cycloalkyl, optionally substituted heterocyclyl, optionally substituted cycloalkylalkyl, optionally substituted cycloalkyl-O-, optionally substituted aryl, optionally substituted aralkyl, optionally substituted heteroaryl, optionally substituted heteroaralkyl, optionally substituted aryloxy, optionally substituted aralkyloxy, optionally substituted heteroaryloxy, optionally substituted heteroaralkyloxy, $-N(R^{22})_2$, $-SO_2R^{21}$, $-N(R^{22})SO_2R^{21}$, $-SO_2N(R^{22})_2$, $-N(R^{22})SO_2N(R^{22})_2$, $-CON(R^{22})_2$, $-N(R^{22})CO_2R^{21}$, $-N(R^{22})CON(R^{22})_2$, $-N(R^{22})COR^{21}$, $-OC(O)N(R^{22})_2$, $-OSO_2N(R^{22})_2$, or $-N(R^{22})SO_3R^{21}$;

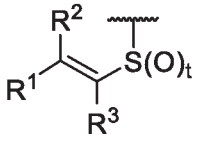
R^{17} is selected from hydrogen, halogen, -CN, optionally substituted alkyl, optionally substituted alkoxy, optionally substituted cycloalkyl, optionally substituted heterocyclyl, optionally substituted cycloalkylalkyl, optionally substituted cycloalkyl-O-, optionally substituted aryl, optionally substituted aralkyl, optionally substituted heteroaryl, optionally substituted heteroaralkyl, optionally substituted aryloxy, optionally substituted aralkyloxy, optionally substituted heteroaryloxy, optionally substituted heteroaralkyloxy, $-N(R^{22})_2$, $-SO_2R^{21}$, $-N(R^{22})SO_2R^{21}$, $-SO_2N(R^{22})_2$, $-N(R^{22})SO_2N(R^{22})_2$, $-CON(R^{22})_2$, $-N(R^{22})CO_2R^{21}$, $-N(R^{22})CON(R^{22})_2$, $-N(R^{22})COR^{21}$, $-OC(O)N(R^{22})_2$, $-OSO_2N(R^{22})_2$, or $-N(R^{22})SO_3R^{21}$;

R^{18} is selected from hydrogen, halogen, -CN, optionally substituted alkyl, optionally substituted alkoxy, optionally substituted cycloalkyl, optionally substituted heterocyclyl, optionally substituted cycloalkylalkyl, optionally substituted cycloalkyl-O-, optionally substituted aryl, optionally substituted aralkyl, optionally substituted heteroaryl, optionally substituted heteroaralkyl, optionally substituted aryloxy, optionally substituted aralkyloxy, optionally substituted heteroaryloxy, optionally substituted heteroaralkyloxy, $-N(R^{22})_2$, $-SO_2R^{21}$, $-N(R^{22})SO_2R^{21}$, $-SO_2N(R^{22})_2$, $-N(R^{22})SO_2N(R^{22})_2$, $-CON(R^{22})_2$, $-N(R^{22})CO_2R^{21}$, $-N(R^{22})CON(R^{22})_2$, $-N(R^{22})COR^{21}$, $-OC(O)N(R^{22})_2$, $-OSO_2N(R^{22})_2$, or $-N(R^{22})SO_3R^{21}$;

each R^{21} is independently selected from alkyl, cycloalkyl, cycloalkylalkyl, aryl, aralkyl, heterocyclyl, heterocyclylalkyl, heteroaryl, or heteroarylalkyl; and

each R^{22} is independently selected from hydrogen, alkyl, cycloalkyl, cycloalkylalkyl, aryl, aralkyl, heterocyclyl, heterocyclylalkyl, heteroaryl, or heteroarylalkyl.

74. The compound of claim 73, or pharmaceutically acceptable salt or solvate thereof, wherein G is .

75. The compound of claim 73, or pharmaceutically acceptable salt or solvate thereof, wherein G is .

76. The compound of claim 74 or 75 or pharmaceutically acceptable salt or solvate thereof, wherein R^3 is hydrogen or –CN.

77. The compound of claim 73 or 75, or pharmaceutically acceptable salt or solvate thereof, wherein t is 2.

78. The compound of claim 73, or pharmaceutically acceptable salt or solvate thereof, wherein W is O.

79. The compound of claim 73, or pharmaceutically acceptable salt or solvate thereof, wherein W is $–CH_2-$.

80. The compound of claim 73, or pharmaceutically acceptable salt or solvate thereof, wherein W is NH or NR^{12}.

81. The compound of claim 73, or pharmaceutically acceptable salt or solvate thereof, wherein W is SO_2.

82. The compound of claim 73, or pharmaceutically acceptable salt or solvate thereof, wherein W is absent.

83. The compound of any one of claims 73-82, or pharmaceutically acceptable salt or solvate thereof, wherein R^2 is hydrogen.

84. The compound of any one of claims 73-83, or pharmaceutically acceptable salt or solvate thereof, wherein R^3 is hydrogen.

85. The compound of any one of claims 73-83, or pharmaceutically acceptable salt or solvate thereof, wherein R^2 and R^3 is hydrogen.

86. The compound of any one of claims 73-85, or pharmaceutically acceptable salt or solvate thereof, wherein R^1 is hydrogen.

87. The compound of any one of claims 73-85, or pharmaceutically acceptable salt or solvate thereof, wherein R^1 is optionally substituted C1-C4 alkyl.

88. The compound of any one of claims 73-85, or pharmaceutically acceptable salt or solvate thereof, wherein R^1 is optionally substituted C1-C2 alkyl.

89. The compound of any one of claims 73-85, or pharmaceutically acceptable salt or solvate thereof, wherein R^1 is optionally substituted C1 alkyl.

90. The compound of claim 89, or pharmaceutically acceptable salt or solvate thereof, wherein the C1 alkyl is substituted with an optionally substituted amino group.

91. The compound of claim 90, or pharmaceutically acceptable salt or solvate thereof, wherein the optionally substituted amino group is a dimethylamino.

92. The compound of any one of claims 73-85, or 87-91, or pharmaceutically acceptable salt or solvate thereof, wherein R^1 is $–CH_2\text{-}N(Me)_2$.

93. The compound of any one of claims 73-85, or pharmaceutically acceptable salt or solvate thereof, wherein R^1 is optionally substituted heterocyclylalkyl.

94. The compound of claim 93, or pharmaceutically acceptable salt or solvate thereof, wherein the optionally substituted heterocyclylalkyl comprises an optionally substituted C1 alkyl.

95. The compound of claim 93 or 94, or pharmaceutically acceptable salt or solvate thereof, wherein the optionally substituted heterocyclylalkyl comprises an optionally substituted N-linked heterocyclyl.

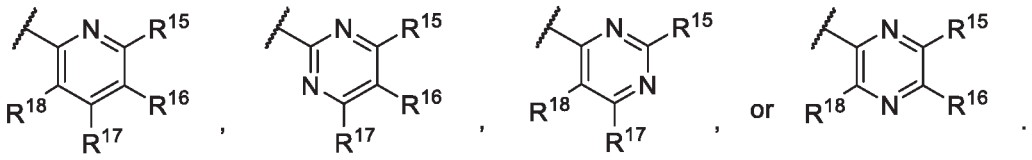
96. The compound of claim 95, or pharmaceutically acceptable salt or solvate thereof, wherein the optionally substituted N-linked heterocyclyl is an N-linked pyrrolidine or piperidine.

97. The compound of any one of claims 73-96, or pharmaceutically acceptable salt or solvate thereof, wherein n is 1 and m is 1.

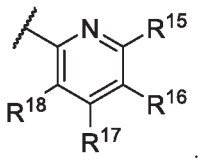
98. The compound of any one of claims 73-96, or pharmaceutically acceptable salt or solvate thereof, wherein n is 1 and m is 2.

99. The compound of any one of claims 73-96, or pharmaceutically acceptable salt or solvate thereof, wherein n is 1 and m is 3.

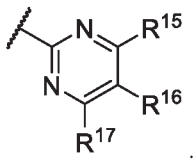
100. The compound of any one of claims 73-99, or pharmaceutically acceptable salt or solvate thereof, wherein Y is selected from:



101. The compound of any one of claims 73-100, or pharmaceutically acceptable salt or solvate thereof, wherein Y is:



102. The compound of any one of claims 73-100, or pharmaceutically acceptable salt or solvate thereof, wherein Y is:



103. The compound of any one of claims 100-102, or pharmaceutically acceptable salt or solvate thereof, wherein R^{15} is hydrogen.

104. The compound of any one of claims 100-102, or pharmaceutically acceptable salt or solvate thereof, wherein R^{16} is hydrogen.

105. The compound of any one of claims 100-102, or pharmaceutically acceptable salt or solvate thereof, wherein R^{17} is hydrogen.

106. The compound of any one of claims 100-102, or pharmaceutically acceptable salt or solvate thereof, wherein R^{18} is hydrogen.

107. The compound of any one of claims 100-102, or pharmaceutically acceptable salt or solvate thereof, wherein R^{15} and R^{16} are hydrogen.

108. The compound of any one of claims 1-107, or pharmaceutically acceptable salt or solvate thereof, wherein E is a bond.

109. The compound of any one of claims 1-107, or pharmaceutically acceptable salt or solvate thereof, wherein E is $-SO_2-$.

110. The compound of any one of claims 1-107, or pharmaceutically acceptable salt or solvate thereof, wherein E is -C(O)-.

111. The compound of any one of claims 1-107, or pharmaceutically acceptable salt or solvate thereof, wherein E is $-CH_2-$.

112. The compound of any one of claims 1-107, or pharmaceutically acceptable salt or solvate thereof, wherein E is $-CH(R^4)-$.

113. The compound of any one of claims 1-107, or pharmaceutically acceptable salt or solvate thereof, wherein E is $-C(R^4)_2-$.

114. A compound, or pharmaceutically acceptable salt or solvate thereof, selected from a compound presented in Table 1.

115. A compound, or pharmaceutically acceptable salt or solvate thereof, selected from a compound presented in Table 2.

116. A compound, or pharmaceutically acceptable salt or solvate thereof, selected from a compound presented in Table 3.

117. A pharmaceutical composition comprising a compound of Formula (I) as described in any one of claims 1-36 or 108-113, or pharmaceutically acceptable salt or solvate thereof, and a pharmaceutically acceptable excipient.

118. A pharmaceutical composition comprising a compound of Formula (II) as described in any one of claims 37-72 or 108-113, or pharmaceutically acceptable salt or solvate thereof, and a pharmaceutically acceptable excipient.

119. A pharmaceutical composition comprising a compound of Formula (III) as described in any one of claims 73-113, or pharmaceutically acceptable salt or solvate thereof, and a pharmaceutically acceptable excipient.

120. A pharmaceutical composition comprising a compound as described in any one of claims 114-116, or pharmaceutically acceptable salt or solvate thereof, and a pharmaceutically acceptable excipient.

121. A method of preparing a pharmaceutical composition comprising mixing a compound of any one of claims 1-113, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier.

122. A compound of any one of claims 1-113, or a pharmaceutically acceptable salt thereof, for use in a method of treatment of the human or animal body.

123. A compound of any one of claims 1-113, or a pharmaceutically acceptable salt thereof, for use in a method of treatment of cancer, neoplastic disease, or hyperproliferative disorder.

124. Use of a compound of any one of claims 1-113, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for the treatment of cancer or neoplastic disease.

125. A method of treating a disease or disorder in a patient in need thereof comprising administering to the patient a compound of Formula (I) as described in any one of claims 1-36 or 108-113, or pharmaceutically acceptable salt or solvate thereof.

126. A method of treating a disease or disorder in a patient in need thereof comprising administering to the patient a compound of Formula (II) as described in any one of claims 37-72 or 108-113, or pharmaceutically acceptable salt or solvate thereof.

127. A method of treating a disease or disorder in a patient in need thereof comprising administering to the patient a compound of Formula (III) as described in any one of claims 73-113, or pharmaceutically acceptable salt or solvate thereof.

128. A method of treating a disease or disorder in a patient in need thereof comprising administering to the patient a compound of any one of claims 114-116, or pharmaceutically acceptable salt or solvate thereof.

129. A method of treating cancer in a patient in need thereof comprising administering to the patient a compound of Formula (I) as described in any one of claims 1-36 or 108-113, or pharmaceutically acceptable salt or solvate thereof.

130. A method of treating cancer in a patient in need thereof comprising administering to the patient a compound of Formula (II) as described in any one of claims 37-72 or 108-113, or pharmaceutically acceptable salt or solvate thereof.

131. A method of treating cancer in a patient in need thereof comprising administering to the patient a compound of Formula (III) as described in any one of claims 73-113, or pharmaceutically acceptable salt or solvate thereof.

132. A method of treating cancer in a patient in need thereof comprising administering to the patient a compound of any one of claims 114-116, or pharmaceutically acceptable salt or solvate thereof.

133. A method of treating cancer in a patient in need thereof comprising administering to the patient a pharmaceutical composition comprising a compound of Formula (I) as described in any one of claims 1-36 or 108-113, or pharmaceutically acceptable salt or solvate thereof, and a pharmaceutically acceptable excipient.

134. A method of treating cancer in a patient in need thereof comprising administering to the patient a pharmaceutical composition comprising a compound of Formula (II) as described in any one of claims 37-72 or 108-113, or pharmaceutically acceptable salt or solvate thereof, and a pharmaceutically acceptable excipient.

135. A method of treating cancer in a patient in need thereof comprising administering to the patient a pharmaceutical composition comprising a compound of Formula (II) as described in any one of claims 73-113, or pharmaceutically acceptable salt or solvate thereof, and a pharmaceutically acceptable excipient.

136. A method of treating cancer in a patient in need thereof comprising administering to the patient a pharmaceutical composition comprising a compound of any one of claims 114-116, or pharmaceutically acceptable salt or solvate thereof, and a pharmaceutically acceptable excipient.

137. A method of inhibiting CDK12 enzyme comprising contacting the enzyme with a compound of any one of claims 1-116.