PYRIMIDINE-FUSED RING COMPOUND, AND PREPARATION METHOD THEREFOR AND USE THEREOF

TECHNICAL FIELD

The present invention belongs to the field of medicines, and specifically to a class of pyrimidine-fused ring compounds and a preparation method and use thereof.

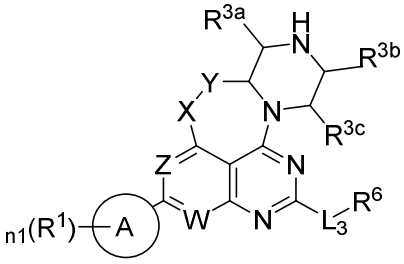
BACKGROUND

KRAS is a 21 kD member of the Ras family of GTPase proteins and is an essential component for cellular signaling. The role of KRAS in malignant tumors and mutations in various types of tumors (e.g., G12C mutation, G12D mutation, and G12V mutation, etc.) are widely known, and thus KRAS has become a very attractive target for cancer treatment in the pharmaceutical industry. Compounds that inhibit KRAS activity are highly desirable for researchers in this field and are under intensive research. At present, breakthroughs are made for KRAS G12C in this field. For example, the KRAS G12C inhibitors of AMG and MIRATI have shown sufficient safety and efficacy. However, there is still constant interest and effort in developing KRAS inhibitors, especially inhibitors that activate KRAS mutants, particularly KRAS G12D.

SUMMARY

The present disclosure provides a class of novel pyrimidine-fused ring compounds, which can be used as KRAS G12D inhibitors and have the advantages of high activity, good selectivity and low toxicity and side effects. The present disclosure also provides a class of novel pyrimidine-fused ring compounds, which will serve as KRAS G12D inhibitors with better bioavailability and higher AUC.

A first example of the present disclosure provides a compound represented by Formula (A) or a pharmaceutically acceptable salt, stereoisomer or solvate thereof:



(A)

where in the formula,

X is O, S or NR^{11}, in which R^{11} is selected from H, C1-C6 alkyl, C1-C6 deuterated alkyl and cycloalkyl;

Y is $CR^{12}R^{13}$, $CR^{14}R^{15}CR^{16}R^{17}$, C(O) or $C(O)CR^{18}R^{19}$, where

R^{12} and R^{13} are each independently selected from H, halogen, hydroxyl, nitro, cyano, C1-C6 alkyl, C1-C6 deuterated alkyl, C1-C6 haloalkyl, C1-C6 alkoxy, C1-C6 haloalkoxy,

C1-C3 alkyl-hydroxyl, heterocyclyl (for example, a 3- to 6-membered heterocyclyl), cyano, -phenyl, -phenyl-SO_2F, -O-phenyl, -O-phenyl-SO_2F, -NHC(O)phenyl, -NHC(O)phenyl-SO_2F, C1-C3 alkyl substituted pyrazolyl, aryl-C1-C3 alkyl-, t-butyldimethylsilylCH_2-, -N(R^{34})$_2$, (C1-C3 alkoxy)C1-C3 alkyl, (C1-C3 alkyl)C(O), oxo, (C1-C3 haloalkyl)C(O)-, -SO_2F, (C1-C3 alkoxy)C1-C3 alkoxy, -CH_2OC(O)N(R^{34})$_2$, -CH_2NHC(O)OC1-C6 alkyl, -CH_2NHC(O)N(R^{34})$_2$, -CH_2NHC(O)C1-C6 alkyl, -CH_2(pyrazolyl), -CH_2NHSO_2C1-C6 alkyl, -CH_2OC(O)heterocyclyl, -OC(O)N(R^{34})$_2$, -OC(O)NH(C1-C3 alkyl)O(C1-C3 alkyl), -OC(O)NH(C1-C3 alkyl)O(C1-C3 alkyl)phenyl(C1-C3 alkyl)N(CH_3)$_2$, -OC(O)NH(C1-C3 alkyl)O(C1-C3 alkyl)phenyl, -OC(O)heterocyclyl (for example, -OC(O)-3- to 6-membered heterocyclyl) or -CH_2heterocyclyl (for example, -CH_2-3- to 6-membered heterocyclyl), where the phenyl in the -NHC(O)phenyl or -OC(O)NH(C1-C3 alkyl)O(C1-C3 alkyl)phenyl is optionally substituted with-C(O)H or OH; the heterocyclyl in the -CH_2heterocyclyl is optionally substituted with oxo; and the hydrogen atom on the -C1-C3 alkyl- is substituted with 1 or 2 groups selected from halogen, deuterium, C1-C3 alkyl, and C1-C3 haloalkyl;

R^{36} is each independently halogen, hydroxyl, HC(O)-, C1-C4 alkyl, C1-C4 alkoxy, C1-C4 haloalkyl, C1-C4 hydroxylalkyl or -N(R^{34})$_2$; and

R^{34} is each independently hydrogen, C1-C3 alkyl or C1-C3 haloalkyl; or two R^{34}, together with the nitrogen atom to which they are attached, form a 3- to 6-membered nitrogen containing heterocyclic group, where the 3- to 6-membered nitrogen containing heterocyclic group is optionally substituted with 1 or 2 groups selected from halogen, methyl, trifluoromethyl, methoxy, and trifluoromethoxy.

In one example, R^{6a} is each independently halogen, hydroxyl, C1-C6 hydroxylalkyl, C1-C6 alkyl, C2-C6 alkenyl, C2-C6 haloalkenyl, C2-C6 alkynyl, C2-C6 haloalkynyl, C1-C6 haloalkyl, C1-C6 alkoxy, C1-C6 haloalkoxy, C3-C6 cycloalkyl, cyano, -Q-phenyl, -Q-phenyl-SO_2F, -NHC(O)phenyl, -NHC(O)phenyl-SO_2F, C1-C3 alkyl substituted pyrazolyl, aryl-C1-C3 alkyl-, t-butyldimethylsilyloxyCH_2-, -N(R^{6b})$_2$, (C1-C3 alkoxy)C1-C3 alkyl, (C1-C3 alkyl)C(O)-, oxo, (C1-C3 haloalkyl)C(O)-, -SO_2F, (C1-C3 alkoxy)C1-C3 alkoxy, -CH_2OC(O)N(R^{6b})$_2$, -CH_2NHC(O)OC1-C6 alkyl, -CH_2NHC(O)N(R^{6b})$_2$, -CH_2NHC(O)C1-C6 alkyl, -CH_2(pyrazolyl), -CH_2NHSO_2C1-C6 alkyl, -C1-C3 alkyl-OC(O)heterocyclyl, -OC(O)N(R^{6b})$_2$, -OC(O)NH(C1-C3 alkyl)O(C1-C3 alkyl), -OC(O)NH(C1-C3 alkyl)O(C1-C3 alkyl)phenyl(C1-C3 alkyl)N(CH_3)$_2$, -OC(O)NH(C1-C3 alkyl)O(C1-C3 alkyl)phenyl, -OC(O)heterocyclyl, -OC(O)C1-C6 alkyl, -OC(O)C1-C6 haloalkyl, -C1-C3 alkyl-OC(O)C1-C6 alkyl, -C1-C3 alkyl-OC(O)C1-C6 haloalkyl, -OC(O)phenyl, -C1-C3 alkyl-OC(O)phenyl or -CH_2heterocyclyl, where the phenyl involved in the above groups is optionally substituted with-C(O)H or OH; the heterocyclyl in -C1-C3 alkyl-heterocyclyl is optionally substituted with oxo; Q is a bond

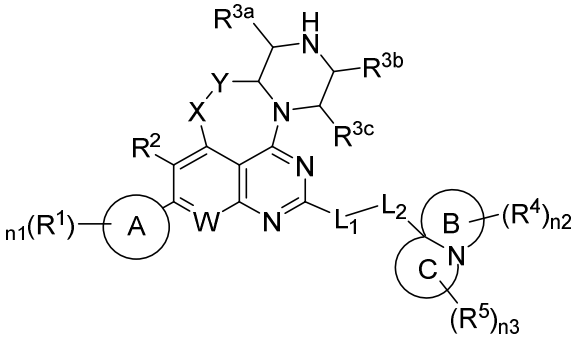
or O; R^{6b} is each independently hydrogen, C1-C6 alkyl, C1-C6 deuterated alkyl or C1-C6 haloalkyl; or two R^{6b} each independently form, together with the nitrogen atom to which they are attached, a 3- to 6-membered nitrogen containing heterocyclic group, where the 3- to 6-membered nitrogen containing heterocyclic group is optionally substituted with 1 or 2 groups selected from halogen, methyl, trifluoromethyl, methoxy, and trifluoromethoxy; and the C3-C6 cycloalkyl is optionally substituted with 1 or 2 C1-C6 alkyl.

In one example, R^{6a} is each independently halogen, hydroxyl, C1-C3 hydroxylalkyl, C1-C3 alkyl, C2-C4 alkenyl, haloC2-C4 alkenyl, C2-C4 alkynyl, haloC2-C4 alkynyl, C1-C3 haloalkyl, C1-C3 alkoxy, C1-C3 haloalkoxy, C3-C6 cycloalkyl, cyano, -Q-phenyl, -Q-phenyl-SO_2F, -NHC(O)phenyl, -NHC(O)phenyl-SO_2F, C1-C3 alkyl substituted pyrazolyl, aryl-C1-C3 alkyl-, t-butyldimethylsilyloxyCH_2-, -N(R^{6b})$_2$, (C1-C3 alkoxy)C1-C3 alkyl, (C1-C3 alkyl)C(O)-, oxo, (C1-C3 haloalkyl)C(O)-, -SO_2F, (C1-C3 alkoxy)C1-C3 alkoxy, -CH_2OC(O)N(R^{6b})$_2$, -CH_2NHC(O)OC1-C3 alkyl, -CH_2NHC(O)N(R^{6b})$_2$, -CH_2NHC(O)C1-C3 alkyl, -CH_2(pyrazolyl), -CH_2NHSO$_2$C1-C3 alkyl, -C1-C3 alkyl-OC(O)heterocyclyl, -OC(O)N(R^{6b})$_2$, -OC(O)NH(C1-C3 alkyl)O(C1-C3 alkyl), -OC(O)NH(C1-C3 alkyl)O(C1-C3 alkyl)phenyl(C1-C3 alkyl)N(CH_3)$_2$, -OC(O)NH(C1-C3 alkyl)O(C1-C3 alkyl)phenyl, -OC(O)heterocyclyl, -OC(O) C1-C3 alkyl, -OC(O)C1-C3 haloalkyl, -C1-C3 alkyl-OC(O)C1-C3 alkyl, -C1-C3 alkyl-OC(O)C1-C3 haloalkyl, -OC(O)phenyl, -C1-C3 alkyl-OC(O)phenyl or -CH_2heterocyclyl, where the phenyl involved in the above groups is optionally substituted with-C(O)H or OH; the heterocyclyl in the -C1-C3 alkyl-heterocyclyl is optionally substituted with oxo; Q is a bond or O; R^{6b} is each independently hydrogen, C1-C3 alkyl, C1-C3 deuterated alkyl or C1-C3 haloalkyl; or two R^{6b} each independently form, together with the nitrogen atom to which they are attached, a 3- to 6-membered nitrogen containing heterocyclic group, where the 3- to 6-membered nitrogen containing heterocyclic groupis optionally substituted with 1 or 2 groups selected from halogen, methyl, trifluoromethyl, methoxy, and trifluoromethoxy; and the C3-C6 cycloalkyl is optionally substituted with 1 or 2 C1-C6 alkyl.

In one example, R^{6a} is each independently halogen, hydroxyl, C1-C3 alkyl, C2-C4 alkenyl, C2-C4 haloalkenyl, C2-C4 alkynyl, C1-C3 haloalkyl, C3-C6 cycloalkyl, cyano, -N(R^{6b})$_2$, where R^{6b} is each independently hydrogen, C1-C3 alkyl, C1-C3 deuterated alkyl or C1-C3 haloalkyl; or two R^{6b} each independently form, together with the nitrogen atom to which they are attached, a 3- to 6-membered nitrogen containing heterocyclic group, where the 3- to 6-membered nitrogen containing heterocyclic group is optionally substituted with 1 or 2 groups selected from halogen, methyl, trifluoromethyl, methoxy, and trifluoromethoxy; and the C3-C6 cycloalkyl is optionally substituted with 1 or 2 methyl.

In one example, R^{6a} is each independently halogen, hydroxyl, methyl, ethyl, propyl, ethenyl, haloethenyl (for example, monofluoroethenyl, and difluoroethenyl), ethynyl, propynyl, halomethyl, haloethyl, cyclopropyl, cyano, or $-N(R^{6b})_2$, where R^{6b} is each independently hydrogen or methyl; and the cyclopropyl is optionally substituted with 1 or 2 methyl.

In some examples, the compound is represented by Formula (I):



(I)

where in the formula,

X, Y, W, ring A, R^1, n1, and R^2 are each as defined above;

R^{3a}, R^{3b}, and R^{3c} are each independently hydrogen, halogen, hydroxyl, cyano, C1-C3 alkyl, C1-C3 deuterated alkyl or C1-C3 haloalkyl;

L_1 is a bond, O or NR^{34};

L_2 is C1-C4 alkylene or heteroaryl, where 1 or 2 hydrogen atom(s) on any carbon atom(s) in the C1-C4 alkylene is/are optionally each independently substituted with deuterium, C1-C6 alkyl or C1-C6 haloalkyl; or 2 hydrogen atoms on any carbon atom in the C1-C4 alkylene are optionally both replaced by $-(CH_2)_{m3}-$, $-(CH_2)_{m1}-O-(CH_2)_{m2}-$, or $-(CH_2)_{m1}-N-(CH_2)_{m2}-$, to form a cyclic substituent; m3 is 1 or 2; m1 is each independently 0, 1, 2 or 3; m2 is each independently 0, 1, 2 or 3; and m1 and m2 are not both 0;

ring B is a 3- to 6-membered nitrogen-containing heterocyclic group;

ring C is a 3- to 6-membered nitrogen containing heterocyclic group;

R^4 is a substituent at any position on ring B; n2 is 0, 1, 2 or 3;

R^5 is a substituent at any position on ring C; n3 is 0, 1, 2 or 3;

R^4 and R^5 are defined as follows:

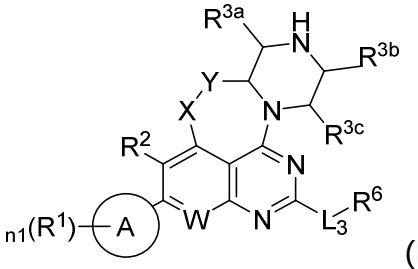
(a) each R^4 and each R^5 are each independently halogen, hydroxyl, C1-C3 hydroxylalkyl, C1-C3 alkyl, C1-C3 haloalkyl, C1-C3 alkoxy, C2-C6 alkenyl, C2-C6 haloalkenyl, C2-C4 alkenylene, C2-C4 halo alkenylene, cyano, -phenyl, -phenyl-SO_2F, -O-phenyl, -O-phenyl-SO_2F, -NHC(O)phenyl, -NHC(O)phenyl-SO_2F, C1-C3 alkyl substituted pyrazolyl, aryl-C1-C3 alkyl-, t-butyldimethylsilylCH_2-, $-N(R^{34})_2$, (C1-C3 alkoxy)C1-C3 alkyl, (C1-C3 alkyl)C(O), oxo, (C1-C3 haloalkyl)C(O)-, $-SO_2F$, (C1-C3 alkoxy)C1-C3 alkoxy, $-CH_2OC(O)N(R^{34})_2$, -

optionally substituted with-C(O)H or OH; and the heterocyclyl in the -CH_2heterocyclyl is optionally substituted with oxo; or

(d) 1 R^4 is -CH_2CH_2- or -$CH_2CH_2CH_2$-, and forms, together with the carbon atom to which it is attached, cyclopropyl or cyclobutyl; 1 R^5 is -CH_2CH_2- or -$CH_2CH_2CH_2$-, and forms, together with the carbon atom to which it is attached, cyclopropyl or cyclobutyl; the remaining R^4 and the remaining R^5 are each independently halogen, hydroxyl, C1-C3 hydroxylalkyl, C1-C3 alkyl, C1-C3 haloalkyl, C2-C4 alkenylene, C2-C4 halo alkenylene, C1-C3 alkoxy, C2-C6 alkenyl, C2-C6 haloalkenyl, cyano, -phenyl, -phenyl-SO_2F, -O-phenyl, -O-phenyl-SO_2F, -NHC(O)phenyl, -NHC(O)phenyl-SO_2F, C1-C3 alkyl substituted pyrazolyl, aryl-C1-C3 alkyl-, t-butyldimethylsilylCH_2-, -N(R^{34})$_2$, (C1-C3 alkoxy)C1-C3 alkyl, (C1-C3 alkyl)C(O), oxo, (C1-C3 haloalkyl)C(O)-, -SO_2F, (C1-C3 alkoxy)C1-C3 alkoxy, -$CH_2OC(O)N(R^{34})_2$, -$CH_2NHC(O)OC1$-C6 alkyl, -$CH_2NHC(O)N(R^{34})_2$, -$CH_2NHC(O)$C1-C6 alkyl, -CH_2(pyrazolyl), -CH_2NHSO_2C1-C6 alkyl, -$CH_2OC(O)$heterocyclyl, -$OC(O)N(R^{34})_2$, -OC(O)NH(C1-C3 alkyl)O(C1-C3 alkyl), -OC(O)NH(C1-C3 alkyl)O(C1-C3 alkyl)phenyl(C1-C3 alkyl)N(CH_3)$_2$, -OC(O)NH(C1-C3 alkyl)O(C1-C3 alkyl)phenyl, -OC(O)heterocyclyl or -CH_2heterocyclyl, where the phenyl in the -NHC(O)phenyl or -OC(O)NH(C1-C3 alkyl)O(C1-C3 alkyl)phenyl is optionally substituted with-C(O)H or OH; and the heterocyclyl in the -CH_2heterocyclyl is optionally substituted with oxo;

R^{34} is each independently hydrogen, C1-C3 alkyl or C1-C3 haloalkyl; or two R^{34}, together with the nitrogen atom to which they are attached, form a 3- to 6-membered nitrogen containing heterocyclic group, where the 3- to 6-membered nitrogen containing heterocyclic groupis optionally substituted with 1 or 2 groups selected from halogen, methyl, trifluoromethyl, methoxy, and trifluoromethoxy.

In some examples, the compound is represented by Formula (I):



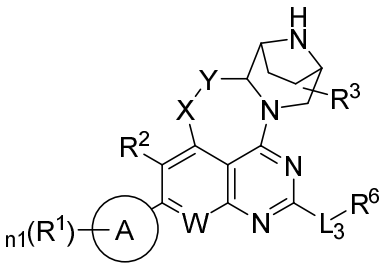
(II)

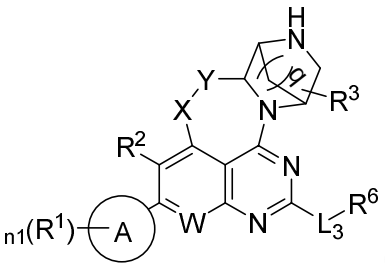
where in the formula, X, Y, W, ring A, R^1, n1, R^2, L_3, and R^6 are each as defined above;

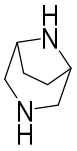
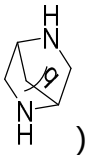
R^{3a} and R^{3b} are linked to form -CHR^{3a1}- or -$CHR^{3a2}CHR^{3a3}$-; and R^{3c} is hydrogen, halogen, hydroxyl, cyano, C1-C3 alkyl, C1-C3 deuterated alkyl or C1-C3 haloalkyl, where R^{3a1}, R^{3a2}, and R^{3a3} are each independently hydrogen, halogen, hydroxyl, cyano, C1-C3 alkyl, C1-C3 deuterated alkyl or C1-C3 haloalkyl; or

R^{3a} and R^{3c} are linked to form -CHR^{3a1}- or -$CHR^{3a2}CHR^{3a3}$-; and R^{3b} is hydrogen, halogen, hydroxyl, cyano, C1-C3 alkyl, C1-C3 deuterated alkyl or C1-C3 haloalkyl, where R^{3a1}, R^{3a2}, and R^{3a3} are each independently hydrogen, halogen, hydroxyl, cyano, C1-C3 alkyl, C1-C3 deuterated alkyl or C1-C3 haloalkyl.

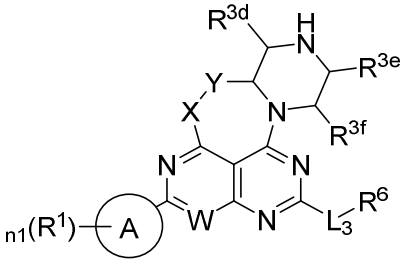
In some examples, the compound is represented by Formula (II-1) or Formula (II-2):


(II-1)


(II-2)

where in each formula, q is 1 or 2; R^3 is substituent at any position on a bridged ring (the bridged ring bearing R^3 herein is generally a bridged ring as shown in  or ) and is each independently hydrogen, halogen, hydroxyl, cyano, C1-C3 alkyl, C1-C3 deuterated alkyl or C1-C3 haloalkyl; and R^1, n1, ring A, R^2, X, Y, W, L_3, and R^6 are each as defined above.

In some examples, the compound is represented by Formula (III):


(III)

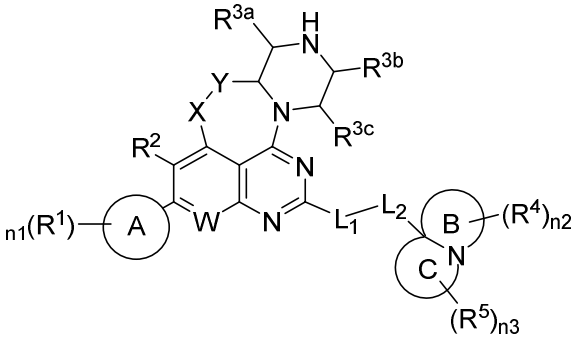
where in the formula, X, Y, W, ring A, R^1, n1, L_3, and R^6 are each as defined above;

R^{3d}, R^{3e}, and R^{3f} are each independently hydrogen, halogen, hydroxyl, cyano, C1-C3 alkyl, C1-C3 deuterated alkyl or C1-C3 haloalkyl; or

R^{3d} and R^{3e} are linked to form -CHR^{3d1}- or -$CHR^{3d2}CHR^{3d3}$-; and R^{3f} is hydrogen, halogen, hydroxyl, cyano, C1-C3 alkyl, C1-C3 deuterated alkyl or C1-C3 haloalkyl, where R^{3d1}, R^{3d2}, and R^{3d3} are each independently hydrogen, halogen, hydroxyl, cyano, C1-C3 alkyl, C1-C3 deuterated alkyl or C1-C3; or

R^{3d} and R^{3f} are linked to form -CHR^{3f1}- or -$CHR^{3f2}CHR^{3f3}$-; and R^{3e} is hydrogen, halogen, hydroxyl, cyano, C1-C3 alkyl, C1-C3 deuterated alkyl or C1-C3 haloalkyl, where R^{3f1}, R^{3f2}, and R^{3f3} are each independently hydrogen, halogen, hydroxyl, cyano, C1-C3 alkyl, C1-C3 deuterated alkyl or C1-C3 haloalkyl.

In one example, the present disclosure provides a compound of Formula (I) or a pharmaceutically acceptable salt, stereoisomer or solvate thereof:



(I)

where in the formula, X is O or NR^{11}, in which R^{11} is selected from H and C1-C6 alkyl;

Y is $CR^{12}R^{13}$, $CR^{14}R^{15}CR^{16}R^{17}$, C(O) or $C(O)CR^{18}R^{19}$, where R^{12}, R^{13}, R^{14} and R^{15} are each independently selected from H, cyano, C1-C3 alkyl, C1-C3 deuterated alkyl, and C1-C3 haloalkyl; and R^{16}, R^{17}, R^{18}, and R^{19} are each independently selected from H, C1-C3 alkyl and halo;

W is N or CR^{20}, where R^{20} is H, cyano, C1-C6 alkyl, halogen, C1-C6 haloalkyl, C1-C6 alkoxy, cycloalkyl, cycloalkyl-O-, heterocyclyl or heterocyclyl-O-, in which the cycloalkyl and the heterocyclyl are each independently substituted with halo;

ring A is selected from the group consisting of aryl and heteroaryl;

R^1 is a substituent at any position on ring A; and R^1 is each independently selected from C1-C6 alkyl, halogen, hydroxyl, C1-C6 alkoxy, C1-C6 haloalkyl, C1-C6 haloalkoxy, cyano, $NR^{21}R^{22}$, $C(O)NR^{23}R^{24}$, CH_2R^{25}, $N=S(O)(C1\text{-}C6\ alkyl)_2$, S(O)C1-C6 alkyl, $S(O)_2R^{26}$, -S-C1-C6 alkyl, C2-C6 alkenyl, C2-C6 alkynyl, C2-C6hydroxyl alkynyl, C1-C6cyano alkyl, triazolyl, -S-C1-C6 haloalkyl, C1-C6 hydroxylalkyl, $-CH_2C(O)NR^{27}R^{28}$, -C2-C6 alkynyl$NR^{29}R^{30}$, C2-C6 deuterated alkynyl, (C1-C6 alkoxy)C1-C6 haloalkyl- or cycloalkyl, where the cycloalkyl is optionally substituted with halo or C1-C6 alkyl, in which

R^{21} is H, C1-C6 alkyl, C1-C6 haloalkyl, C(O)C1-C6 alkyl or C(O)OC1-C6 alkyl; R^{22} is H, C1-C6 alkyl or C1-C6 haloalkyl; or R^{21} and R^{22}, together with the nitrogen atom to which they are attached, form a 3- to 6-membered nitrogen-containing heterocyclic group, where the 3- to 6-membered nitrogen-containing heterocyclic group is optionally substituted with 1 or 2 groups selected from halogen, methyl, trifluoromethyl, methoxy and trifluoromethoxy;

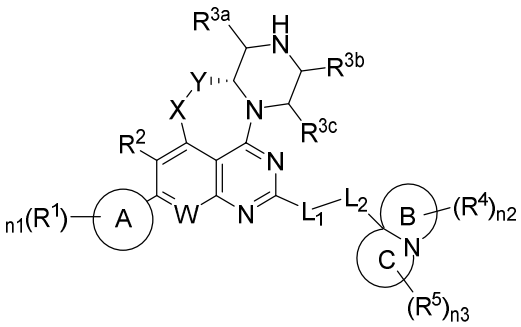
R^{23} and R^{24} are each independently H, C1-C6 alkyl, or C1-C6 haloalkyl; or R^{23} and R^{24}, together with the nitrogen atom to which they are attached, form a 3- to 6-membered nitrogen-containing heterocyclic group, where the 3- to 6-membered nitrogen-containing heterocyclic group is optionally substituted with 1 or 2 groups selected from halogen, methyl, trifluoromethyl, methoxy, and trifluoromethoxy;

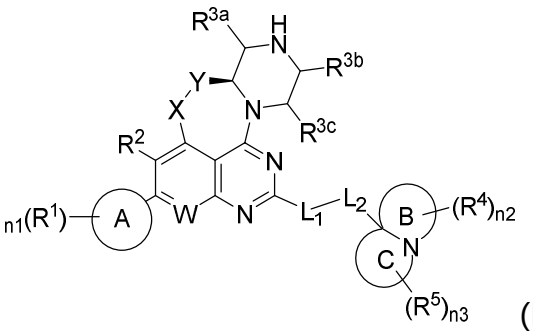
(c) 1 R^5 is $-CH_2CH_2-$ or $-CH_2CH_2CH_2-$, and forms, together with the carbon atom to which it is attached, cyclopropyl or cyclobutyl; the remaining R^5 and each R^4 are each independently halogen, hydroxyl, C1-C3 hydroxylalkyl, C1-C3 alkyl, C1-C3 haloalkyl, C1-C3 alkoxy, cyano, -phenyl, -phenyl-SO_2F, -O-phenyl, -O-phenyl-SO_2F, -NHC(O)phenyl, -NHC(O)phenyl-SO_2F, C1-C3 alkyl substituted pyrazolyl, aryl-C1-C3 alkyl-, t-butyldimethylsilylCH_2-, $-N(R^{34})_2$, (C1-C3 alkoxy)C1-C3 alkyl, (C1-C3 alkyl)C(O), oxo, (C1-C3 haloalkyl)C(O)-, $-SO_2F$, (C1-C3 alkoxy)C1-C3 alkoxy, $-CH_2OC(O)N(R^{34})_2$, $-CH_2NHC(O)OC$1-C6 alkyl, $-CH_2NHC(O)N(R^{34})_2$, $-CH_2NHC(O)C$1-C6 alkyl, $-CH_2$(pyrazolyl), $-CH_2NHSO_2C$1-C6 alkyl, $-CH_2OC(O)$heterocyclyl, $-OC(O)N(R^{34})_2$, -OC(O)NH(C1-C3 alkyl)O(C1-C3 alkyl), -OC(O)NH(C1-C3 alkyl)O(C1-C3 alkyl)phenyl(C1-C3 alkyl)$N(CH_3)_2$, -OC(O)NH(C1-C3 alkyl)O(C1-C3 alkyl)phenyl, -OC(O)heterocyclyl or $-CH_2$heterocyclyl, where the phenyl in the -NHC(O)phenyl or -OC(O)NH(C1-C3 alkyl)O(C1-C3 alkyl)phenyl is optionally substituted with-C(O)H or OH; and the heterocyclyl in the $-CH_2$heterocyclyl is optionally substituted with oxo; or

(d) 1 R^4 is $-CH_2CH_2-$ or $-CH_2CH_2CH_2-$, and forms, together with the carbon atom to which it is attached, cyclopropyl or cyclobutyl; 1 R^5 is $-CH_2CH_2-$ or $-CH_2CH_2CH_2-$, and forms, together with the carbon atom to which it is attached, cyclopropyl or cyclobutyl; the remaining R^4 and the remaining R^5 are each independently halogen, hydroxyl, C1-C3 hydroxylalkyl, C1-C3 alkyl, C1-C3 haloalkyl, C1-C3 alkoxy, cyano, -phenyl, -phenyl-SO_2F, -O-phenyl, -O-phenyl-SO_2F, -NHC(O)phenyl, -NHC(O)phenyl-SO_2F, C1-C3 alkyl substituted pyrazolyl, aryl-C1-C3 alkyl-, t-butyldimethylsilylCH_2-, $-N(R^{34})_2$, (C1-C3 alkoxy)C1-C3 alkyl, (C1-C3 alkyl)C(O), oxo, (C1-C3 haloalkyl)C(O)-, $-SO_2F$, (C1-C3 alkoxy)C1-C3 alkoxy, $-CH_2OC(O)N(R^{34})_2$, $-CH_2NHC(O)OC$1-C6 alkyl, $-CH_2NHC(O)N(R^{34})_2$, $-CH_2NHC(O)C$1-C6 alkyl, $-CH_2$(pyrazolyl), $-CH_2NHSO_2C$1-C6 alkyl, $-CH_2OC(O)$heterocyclyl, $-OC(O)N(R^{34})_2$, -OC(O)NH(C1-C3 alkyl)O(C1-C3 alkyl), -OC(O)NH(C1-C3 alkyl)O(C1-C3 alkyl)phenyl(C1-C3 alkyl)$N(CH_3)_2$, -OC(O)NH(C1-C3 alkyl)O(C1-C3 alkyl)phenyl, -OC(O)heterocyclyl or $-CH_2$heterocyclyl, where the phenyl in the -NHC(O)phenyl or -OC(O)NH(C1-C3 alkyl)O(C1-C3 alkyl)phenyl is optionally substituted with-C(O)H or OH; and the heterocyclyl in the $-CH_2$heterocyclyl is optionally substituted with oxo; and

R^{34} is each independently hydrogen, C1-C3 alkyl or C1-C3 haloalkyl; or two R^{34}, together with the nitrogen atom to which they are attached, form a 3- to 6-membered nitrogen containing heterocyclic group, where the 3- to 6-membered nitrogen containing heterocyclic group is optionally substituted with 1 or 2 groups selected from halogen, methyl, trifluoromethyl, methoxy, and trifluoromethoxy.

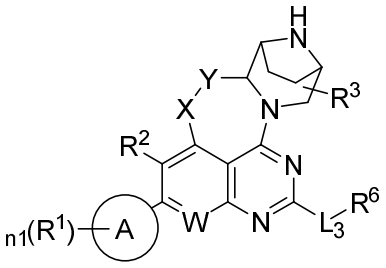
In some examples, the compound is represented by Formula (I-1) or Formula (I-2):

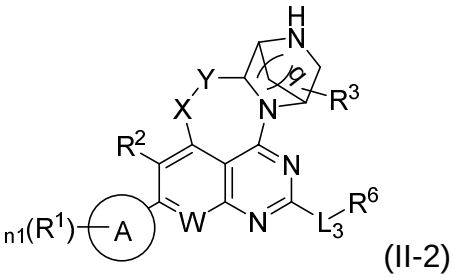

(I-1)


(I-2)

where in each formula, X, Y, W, R^1, R^2, R^{3a}, R^{3b}, R^{3c}, R^4, R^5, n1, n2, n3, L_1, L_2, ring A, ring B, and ring C are each as defined in Formula (I).

In one example, the present disclosure provides a compound of Formula (II-1) or Formula (II-2) or a pharmaceutically acceptable salt, stereoisomer or solvate thereof:


(II-1)


(II-2)

where in each formula,

q is 1 or 2;

X is O or NR^{11}, in which R^{11} is selected from H and C1-C6 alkyl;

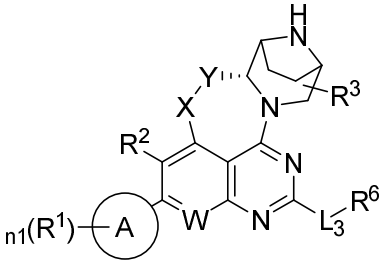
Y is $CR^{12}R^{13}$, $CR^{14}R^{15}CR^{16}R^{17}$, C(O) or $C(O)CR^{18}R^{19}$, where R^{12}, R^{13}, R^{14} and R^{15} are each independently selected from H, cyano, C1-C3 alkyl, C1-C3 deuterated alkyl, and C1-C3 haloalkyl; and R^{16}, R^{17}, R^{18}, and R^{19} are each independently selected from H, C1-C3 alkyl and halo;

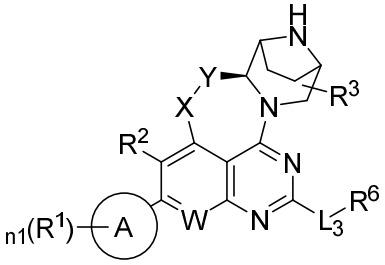
W is N or CR^{20}, where R^{20} is H, cyano, C1-C6 alkyl, halogen, C1-C6 haloalkyl, C1-C6 alkoxy, cycloalkyl, cycloalkyl-O-, heterocyclyl or heterocyclyl-O-, in which the cycloalkyl and the heterocyclyl are each independently substituted with halo;

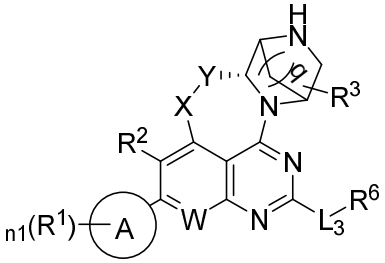
ring A is selected from the group consisting of aryl and heteroaryl;

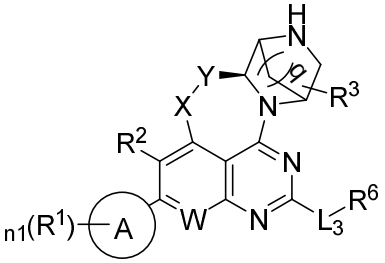
R^1 is a substituent at any position on ring A; and R^1 is each independently selected from C1-C6 alkyl, halogen, hydroxyl, C1-C6 alkoxy, C1-C6 haloalkyl, C1-C6 haloalkoxy, cyano, $NR^{21}R^{22}$, $C(O)NR^{23}R^{24}$, CH_2R^{25}, $N{=}S(O)(C1\text{-}C6\ alkyl)_2$, S(O)C1-C6 alkyl, $S(O)_2R^{26}$, -S-C1-C6 alkyl, C2-C6 alkenyl, C2-C6 alkynyl, C2-C6hydroxyl alkynyl, C1-C6cyano alkyl, triazolyl, -S-C1-C6 haloalkyl, C1-C6 hydroxylalkyl, $-CH_2C(O)NR^{27}R^{28}$, -C2-C6 alkynyl$NR^{29}R^{30}$, C2-C6 deuterated alkynyl, (C1-C6 alkoxy)C1-C6 haloalkyl- or cycloalkyl, where the cycloalkyl is optionally substituted with halo or C1-C6 alkyl, in which

In some examples, the compound is represented by Formula (II-1A), Formula (II-1B), Formula (II-2A), and Formula (II-2B):


(II-1A)

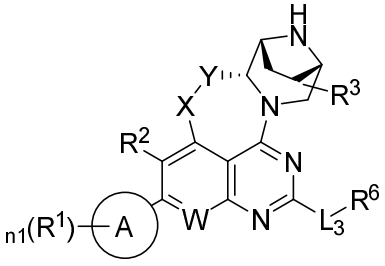

(II-1B)

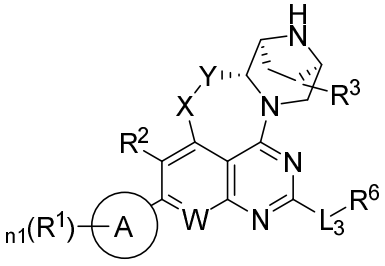

(II-2A)

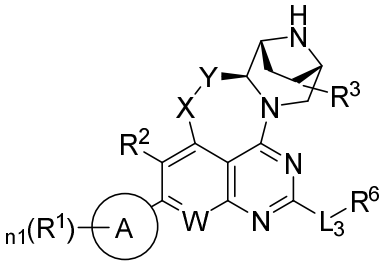

(II-2B)

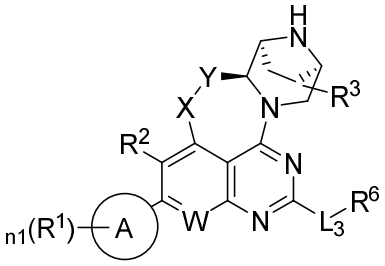
where in each formula, X, Y, W, R^1, R^2, R^3, R^6, n1, L_3, q, and ring A are each as defined in Formula (II-1) or Formula (II-2).

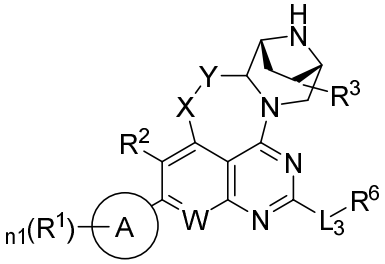
In one example, the compound is represented by Formula (II-1A1), formula (II-1A2), Formula (II-1B1), Formula (II-1B2), Formula (II-1C1) or Formula (II-1C2):

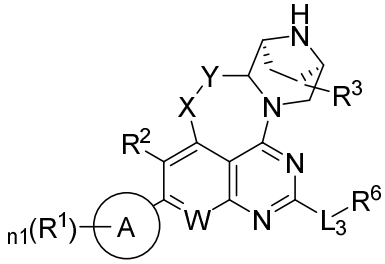

(II-1A1)


(II-1A2)


(II-1B1)

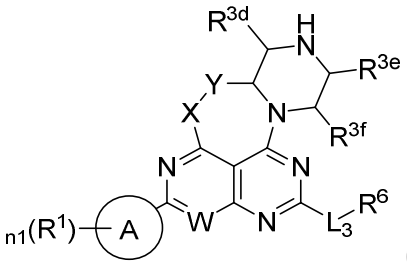

(II-1B2)


(II-1C1)


(II-1C2)

where in each formula, X, Y, W, R^1, R^2, R^3, R^6, n1, L_3, and ring A are each as defined in Formula (II-1) or Formula (II-2).

In one example, the present disclosure provides a compound of Formula (III) or a pharmaceutically acceptable salt, stereoisomer or solvate thereof:



(III)

where in the formula,

X is O or NR^{11}, in which R^{11} is selected from H and C1-C6 alkyl;

Y is $CR^{12}R^{13}$, $CR^{14}R^{15}CR^{16}R^{17}$, C(O) or $C(O)CR^{18}R^{19}$, where R^{12}, R^{13}, R^{14} and R^{15} are each independently selected from H, cyano, C1-C3 alkyl, C1-C3 deuterated alkyl, and C1-C3 haloalkyl; and R^{16}, R^{17}, R^{18}, and R^{19} are each independently selected from H, C1-C3 alkyl and halo;

W is N or CR^{20}, where R^{20} is H, cyano, C1-C6 alkyl, halogen, C1-C6 haloalkyl, C1-C6 alkoxy, cycloalkyl, cycloalkyl-O-, heterocyclyl or heterocyclyl-O-, in which the cycloalkyl and the heterocyclyl are each independently substituted with halo;

ring A is selected from the group consisting of aryl and heteroaryl;

R^1 is a substituent at any position on ring A; and R^1 is each independently selected from C1-C6 alkyl, halogen, hydroxyl, C1-C6 alkoxy, C1-C6 haloalkyl, C1-C6 haloalkoxy, cyano, $NR^{21}R^{22}$, $C(O)NR^{23}R^{24}$, CH_2R^{25}, $N=S(O)(C1\text{-}C6\ alkyl)_2$, S(O)C1-C6 alkyl, $S(O)_2R^{26}$, -S-C1-C6 alkyl, C2-C6 alkenyl, C2-C6 alkynyl, C2-C6hydroxyl alkynyl, C1-C6cyano alkyl, triazolyl, -S-C1-C6 haloalkyl, C1-C6 hydroxylalkyl, $-CH_2C(O)NR^{27}R^{28}$, -C2-C6 alkynyl$NR^{29}R^{30}$, C2-C6 deuterated alkynyl, (C1-C6 alkoxy)C1-C6 haloalkyl- or cycloalkyl, where the cycloalkyl is optionally substituted with halo or C1-C6 alkyl, in which

R^{21} is H, C1-C6 alkyl, C1-C6 haloalkyl, C(O)C1-C6 alkyl or C(O)OC1-C6 alkyl; R^{22} is H, C1-C6 alkyl or C1-C6 haloalkyl; or R^{21} and R^{22}, together with the nitrogen atom to which they are attached, form a 3- to 6-membered nitrogen-containing heterocyclic group, where the 3- to 6-membered nitrogen-containing heterocyclic group is optionally substituted with 1 or 2 groups selected from halogen, methyl, trifluoromethyl, methoxy and trifluoromethoxy;

R^{23} and R^{24} are each independently H, C1-C6 alkyl, or C1-C6 haloalkyl; or R^{23} and R^{24}, together with the nitrogen atom to which they are attached, form a 3- to 6-membered nitrogen-containing heterocyclic group, where the 3- to 6-membered nitrogen-containing heterocyclic group is optionally substituted with 1 or 2 groups selected from halogen, methyl, trifluoromethyl, methoxy, and trifluoromethoxy;

where L is each independently a bond, C1-C4 alkylene or heteroaryl, in which 1 or 2 hydrogen atom(s) on any carbon atom(s) in the C1-C4 alkylene is/are optionally each independently substituted with deuterium, C1-C6 alkyl, or C1-C6 haloalkyl; or 2 hydrogen atoms on any carbon atom in the C1-C4 alkylene are optionally both replaced by $-(CH_2)_{m3}-$, $-(CH_2)_{m1}-O-(CH_2)_{m2}-$, or $-(CH_2)_{m1}-NR^9-(CH_2)_{m2}-$, to form a cyclic substituent; m3 is 1 or 2; m1 is each independently 0, 1, 2 or 3; m2 is each independently 0, 1, 2 or 3; and m1 and m2 are not both 0;

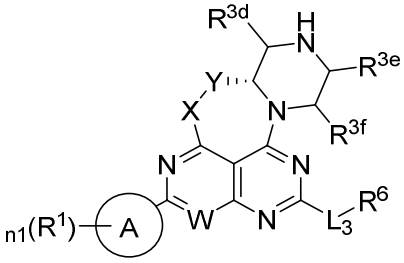
R^9 is hydrogen, C1-C6 alkyl, C1-C6 deuterated alkyl, C1-C6 haloalkyl, C1-C6 alkyl-hydroxyl, C1-C6 alkyl-cyano, C1-C6 alkoxy, C1-C6 alkyl-C1-C6 alkoxy, C3-C6 monocyclic cycloalkyl, C3-C6 deuterated cycloalkyl or C3-C6 halocycloalkyl;

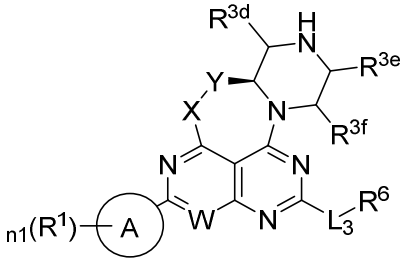
R^{35} is each independently halogen, hydroxyl, C1-C3 alkyl, C1-C3 haloalkyl, C1-C3 alkoxy, C3-C6 cycloalkyl, -C1-C3 alkyl-C1-C3 alkoxy, -C1-C3 alkyl-hydroxyl, heterocyclyl (for example, a 3- to 6-membered heterocyclyl), cyano, -phenyl, -phenyl-SO_2F, -O-phenyl, -O-phenyl-SO_2F, -NHC(O)phenyl, -NHC(O)phenyl-SO_2F, C1-C3 alkyl substituted pyrazolyl, aryl-C1-C3 alkyl-, t-butyldimethylsilylCH_2-, $-N(R^{34})_2$, (C1-C3 alkoxy)C1-C3 alkyl, (C1-C3 alkyl)C(O), oxo, (C1-C3 haloalkyl)C(O)-, $-SO_2F$, (C1-C3 alkoxy)C1-C3 alkoxy, $-CH_2OC(O)N(R^{34})_2$, $-CH_2NHC(O)OC$1-C6 alkyl, $-CH_2NHC(O)N(R^{34})_2$, $-CH_2NHC(O)C$1-C6 alkyl, $-CH_2$(pyrazolyl), $-CH_2NHSO_2C$1-C6 alkyl, $-CH_2OC(O)$heterocyclyl, $-OC(O)N(R^{34})_2$, -OC(O)NH(C1-C3 alkyl)O(C1-C3 alkyl), -OC(O)NH(C1-C3 alkyl)O(C1-C3 alkyl)phenyl(C1-C3 alkyl)$N(CH_3)_2$, -OC(O)NH(C1-C3 alkyl)O(C1-C3 alkyl)phenyl, -OC(O)heterocyclyl (for example, -OC(O)-3- to 6-membered heterocyclyl) or $-CH_2$heterocyclyl (for example, $-CH_2$-3- to 6-membered heterocyclyl), where the phenyl in the -NHC(O)phenyl or -OC(O)NH(C1-C3 alkyl)O(C1-C3 alkyl)phenyl is optionally substituted with-C(O)H or OH; the heterocyclyl in the $-CH_2$heterocyclyl is optionally substituted with oxo; and the hydrogen atom on the -C1-C3 alkyl- is substituted with 1 or 2 groups selected from halogen, deuterium, C1-C3 alkyl, and C1-C3 haloalkyl;

R^{36} is each independently halogen, hydroxyl, HC(O)-, C1-C4 alkyl, C1-C4 alkoxy, C1-C4 haloalkyl, C1-C4 hydroxylalkyl or $-N(R^{34})_2$; and

R^{34} is each independently hydrogen, C1-C3 alkyl or C1-C3 haloalkyl; or two R^{34}, together with the nitrogen atom to which they are attached, form a 3- to 6-membered nitrogen containing heterocyclic group, where the 3- to 6-membered nitrogen containing heterocyclic group is optionally substituted with 1 or 2 groups selected from halogen, methyl, trifluoromethyl, methoxy, and trifluoromethoxy.

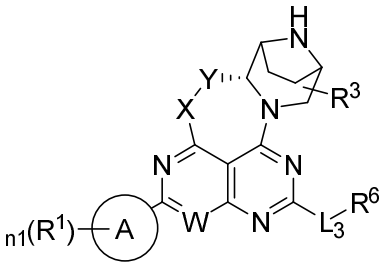
In some examples, the compound is represented by Formula (III-1) or Formula (III-2):

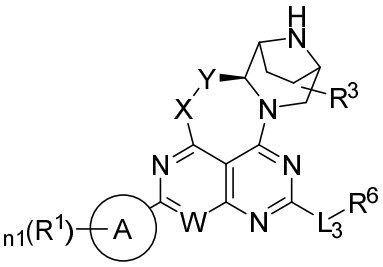

(III-1)

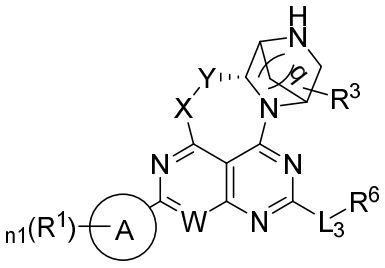

(III-2)

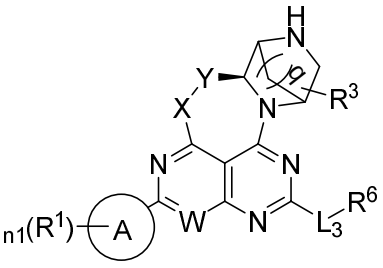
where in each formula, X, Y, W, R^1, R^{3d}, R^{3e}, R^{3f}, R^6, n1, L_3, and ring A are each as defined in Formula (III).

In some examples, the compound is represented by Formula (III-1a), Formula (III-1b), Formula (III-2a), or Formula (III-2b):


(III-1a)

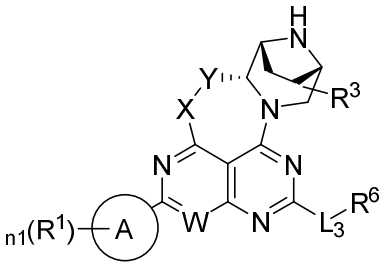

(III-1b)

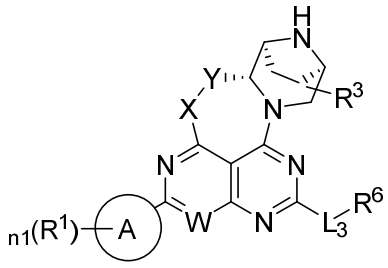

(III-2a)

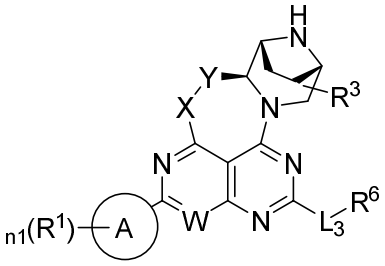

(III-2b)

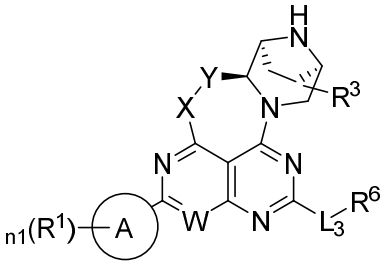
where in each formula, q is 1 or 2; R^3 is a substitutent at any position on a bridged ring and is hydrogen, halogen, hydroxyl, cyano, C1-C3 alkyl, C1-C3 deuterated alkyl or C1-C3 haloalkyl; and X, Y, W, ring A, R^1, n1, L_3, and R^6 are as defined in Formula (III-1) or Formula (III-2).

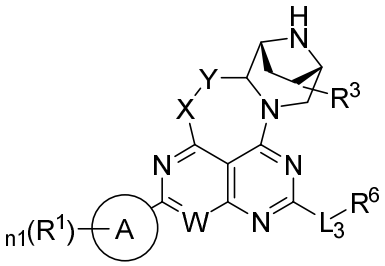
In one example, the compound is represented by Formula (III-1a1), Formula (III-1a2), Formula (III-1b1), Formula (III-1b2), Formula (III-1c1) or Formula (III-1c2):

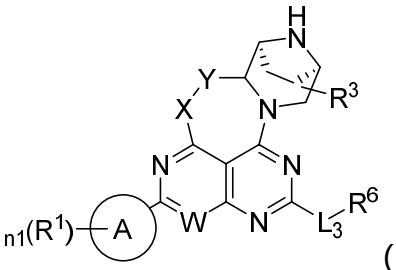

(III-1a1)


(III-1a2)


(III-1b1)


(III-1b2)


(III-1c1)

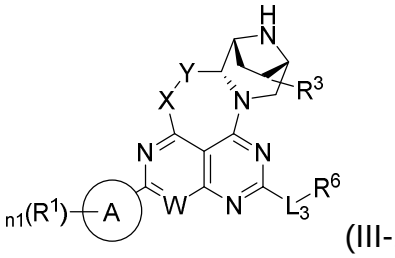

(III-1c2)

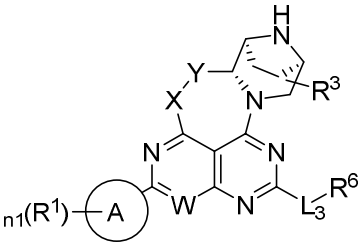
where in each formula, R^3 is a substitutent at any position on a bridged ring and is hydrogen, halogen, hydroxyl, cyano, C1-C3 alkyl, C1-C3 deuterated alkyl or C1-C3 haloalkyl; and X, Y, W, ring A, R^1, n1, L_3, and R^6 are as defined in Formula (III-1) or Formula (III-2).

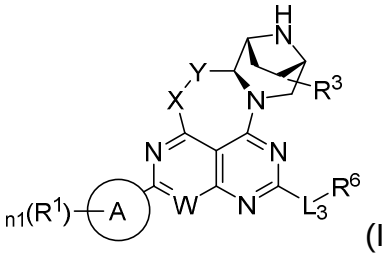
In one example, R^3 is hydrogen.

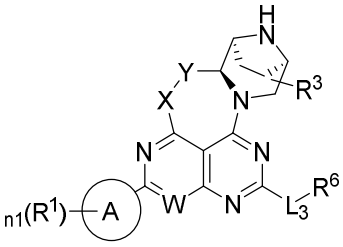
In one example, Y is $-CH_2-$.

In one example, the compound is represented by Formula (III-1a3), Formula (III-1a4), Formula (III-1b3) or Formula (III-1b4):


(III-1a3)


(III-1a4)


(III-1b3)


(III-1b4)

where in each formula,

R^3 is a substitutent at any position on a bridged ring and is hydrogen, halogen, hydroxyl, cyano, C1-C3 alkyl, C1-C3 deuterated alkyl or C1-C3 haloalkyl;

Y is $CR^{12}R^{13}$, $CR^{14}R^{15}CR^{16}R^{17}$, C(O) or $C(O)CR^{18}R^{19}$, where

R^{12} and R^{13} are each independently selected from H, halogen, hydroxyl, nitro, cyano, C1-C6 alkyl, C1-C6 deuterated alkyl, C1-C6 haloalkyl, C1-C6 alkoxy, C1-C6 haloalkoxy,

cycloalkyl, cycloalkyl-O-, heterocyclyl, heterocyclyl-O-, aryl, heteroaryl, aryl-O-, heteroaryl-O-, -C1-C4 alkyl-C1-C6 alkoxy, -C1-C4 alkyl-C1-C6 haloalkoxy, -C1-C4 alkyl-hydroxyl, -C1-C4 alkyl-cyano, and -C1-C4 alkyl-$NR^{121}R^{122}$; R^{12} and R^{13} are not both H; or R^{12} and R^{13}, together with the carbon atom to which they are attached, form a cycloalkyl group;

R^{14} and R^{15} are each independently selected from H, nitro, cyano, C1-C6 alkyl, C1-C6 deuterated alkyl, C1-C6 haloalkyl, C1-C6 alkoxy, C1-C6 haloalkoxy, cycloalkyl, cycloalkyl-O-, heterocyclyl, heterocyclyl-O-, aryl, heteroaryl, aryl-O-, heteroaryl-O-, -C1-C4 alkyl-C1-C6 alkoxy, -C1-C4 alkyl-C1-C6 haloalkoxy, -C1-C4 alkyl-hydroxyl, -C1-C4 alkyl-cyano, -C1-C4 alkyl-$NR^{121}R^{122}$; R^{14} and R^{15} are not both H; or R^{14} and R^{15}, together with the carbon atom to which they are attached, form a cycloalkyl group;

R^{16} and R^{17} are each independently selected from H, halogen, hydroxyl, nitro, cyano, C1-C6 alkyl, C1-C6 deuterated alkyl, C1-C6 haloalkyl, C1-C6 alkoxy, C1-C6 haloalkoxy, cycloalkyl, cycloalkyl-O-, heterocyclyl, heterocyclyl-O-, aryl, heteroaryl, aryl-O-, heteroaryl-O-, -C1-C4 alkyl-C1-C6 alkoxy, -C1-C4 alkyl-C1-C6 haloalkoxy, -C1-C4 alkyl-hydroxyl, -C1-C4 alkyl-cyano, -C1-C4 alkyl-$NR^{121}R^{122}$; and R^{16} and R^{17} are not both H;

R^{18} and R^{19} are each independently selected from H, C1-C3 alkyl and halo;

R^{121} and R^{122} are each independently selected from H and C1-C3 alkyl; or R^{121} and R^{122}, together with the nitrogen atom to which they are attached, form a 3- to 6-membered nitrogen-containing heterocyclic group,

the cycloalkyl, the heterocyclyl, the aryl, the heteroaryl, and the 3- to 6-membered nitrogen-containing heterocyclic group are each independently optionally substituted with a group selected from the group consisting of halogen, hydroxyl, nitro, cyano, C1-C3 alkyl, C1-C3 deuterated alkyl, C1-C3 haloalkyl, C1-C3 alkoxy, and C1-C3 haloalkoxy;

X, W, ring A, R^1, n1, L_3, and R^6 are as defined in Formula (III-1) or Formula (III-2).

In one example, R^3 is hydrogen.

In one example, Y is $CR^{12}R^{13}$, in which R^{12} is selected from halogen, hydroxyl, cyano, C1-C6 alkyl, C1-C6 deuterated alkyl, C1-C6 haloalkyl, C1-C6 alkoxy, C1-C6 haloalkoxy, cycloalkyl, cycloalkyl-O-, heterocyclyl, heterocyclyl-O-, -C1-C4 alkyl-C1-C6 alkoxy, -C1-C4 alkyl-C1-C6 haloalkoxy, -C1-C4 alkyl-hydroxyl, -C1-C4 alkyl-cyano, and -C1-C4 alkyl-$NR^{121}R^{122}$; R^{13} is H; R^{121} and R^{122} are each independently selected from H and C1-C3 alkyl; or R^{121} and R^{122}, together with the nitrogen atom to which they are attached, form a 3- to 6-membered nitrogen-containing heterocyclyl; or R^{12} and R^{13}, together with the carbon atom to which they are attached, form a cycloalkyl group, in which the cycloalkyl, the heterocyclyl, the aryl, the heteroaryl, the 3- to 6-membered nitrogen-containing heterocyclyl are each independently optionally substituted with a group selected from the group consisting of

halogen, hydroxyl, nitro, cyano, C1-C3 alkyl, C1-C3 deuterated alkyl, C1-C3 haloalkyl, C1-C3 alkoxy, and C1-C3 haloalkoxy.

In one example, in Formula (III-1a3), Formula (III-1a4), Formula (III-1b3) or Formula (III-1b4), Y is $CR^{12}R^{13}$, where R^{12} is selected from halogen, hydroxyl, cyano, methyl, ethyl, n-propyl, isopropyl, trideuterated methyl, trifluoromethyl, cyclopropyl, -C1-C4 alkyl-methoxy, -C1-C4 alkyl-hydroxyl, -C1-C4 alkyl-cyano; R^{13} is H; or R^{12} and R^{13}, together with the carbon atom to which they are attached, form a cyclopropyl group.

In one example, in Formula (III-1a3), Formula (III-1a4), Formula (III-1b3) or Formula (III-1b4), Y is -CH(CH_3)-, -CH(CH_2CH_3)-, -CH($CH_2CH_2CH_3$)-, -CH(CH(CH_3)$_2$)-, -CH(cyclopropyl)-, -CH(CH_2OH)-, -CH(CH_2CH_2OH)-, -CH(CH_2CN)-, -CH(CH_2CH_2CN)-, -CH(CH_2CF_3)-, -CH(CH_2CF_2H)-, -CH(CH_2CH_2F)-, -CH(CH_2F)-, -CH(CF_2H)-, -CH(CF_3)-, -CH(CN)-, -CH(CH_2OCH_3)-, , -C(CH_3)$_2$-, or -CH(CD_3)-.

In one example, the cycloalkyl is C3-C20 cycloalkyl. Preferably, the cycloalkyl is C3-C12 cycloalkyl (further preferably C3-C8 monocyclic cycloalkyl), C5-C20 spiro cycloalkyl, C5-C20 fused cycloalkyl or C5-C20 bridged cycloalkyl.

In one example, the heterocyclyl is a 3- to 20-membered heterocyclyl. Preferably, the heterocyclyl is a monocyclic heterocyclyl (for example, a 3- to 8-membered monocyclic heterocyclyl), a 5- to 20-membered spiro heterocyclyl, a 5- to 20-membered fused heterocyclyl, and a 5- to 20-membered bridged heterocyclyl.

In one example, the aryl is C6-C14aryl. Preferably, the aryl is a monocyclic aryl, a non-fused polycyclic aryl, and an aromatic fused polycyclic group.

In one example, the heteroaryl is a 5- to 14-membered heteroaryl. Preferably, the heteroaryl is a monocyclic heteroaryl (for example, a 5- or 6-membered monocyclic heteroaryl), a fused bicyclic heteroaryl (for example, a 8- to 10-membered bicyclic heteroaryl) or a fused tricyclic heteroaryl.

In one example, W is N or CR^{20}, in which R^{20} is H, cyano, C1-C3 alkyl, halogen, C1-C3 haloalkyl, C1-C3 alkoxy, C3-C6 monocyclic cycloalkyl, C3-C6 monocyclic cycloalkyl-O-, a 3- to 6-membered heterocyclyl or a 3- to 6-membered heterocyclyl-O-, in which the C3-C6 monocyclic cycloalkyl and the 3- to 6-membered heterocyclyl are each independently optionally substituted with halo.

In one example, W is N or CR^{20}, in which R^{20} is hydrogen, fluoro, methyl, methoxy or cyclopropyloxy.

In one example, W is N or CR^{20}, in which R^{20} is H, fluoro, chloro, methyl, cyclopropyl, methoxy or cyclopropyloxy.

In one example, X is -N(CH_3)- or -N(cyclopropyl)-.

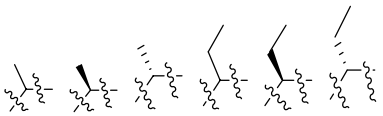
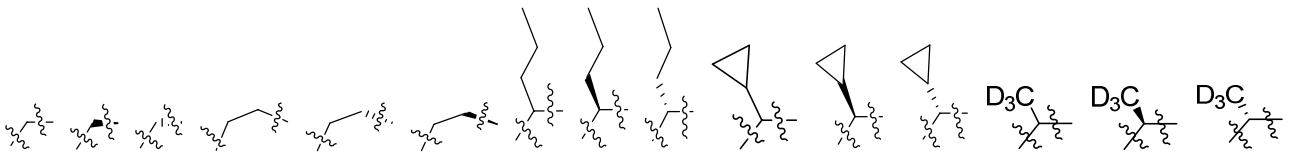
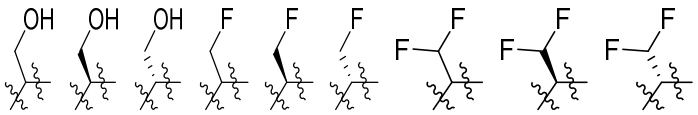
In one example, X is -N(CD_3)-.

In one example, X is O.

In one example, Y is $CR^{12}R^{13}$ or $CR^{14}R^{15}CR^{16}R^{17}$, in which R^{12}, R^{13}, R^{14} and R^{15} are each independently selected from H, cyano, C1-C6 alkyl, C1-C6 haloalkyl, C1-C6 alkoxy, C1-C6 haloalkoxy, C3-C6 monocyclic cycloalkyl, C3-C6 monocyclic cycloalkyl-O-, 3- to 6-membered heterocyclyl, 3- to 6-membered heterocyclyl-O-, phenyl, a 5- or 6-membered heteroaryl, phenyl-O-, 5- or 6-membered heteroaryl-O-, -C1-C2 alkyl-C1-C3 alkoxy, -C1-C2 alkyl-C1-C3 haloalkoxy, -C1-C2 alkyl-hydroxyl, -C1-C2 alkyl-cyano, and -C1-C2 alkyl-$NR^{121}R^{122}$; R^{16} and R^{17} are each independently selected from H; R^{121} and R^{122} are each independently selected from H, and C1-C3 alkyl; or R^{121} and R^{122}, together with the nitrogen atom to which they are attached, form a 3- to 6-membered nitrogen-containing heterocyclyl, in which the C3-C6 monocyclic cycloalkyl, the 3- to 6-membered heterocyclyl, the phenyl, the 5- or 6-membered heteroaryl, and the 3- to 6-membered nitrogen-containing heterocyclyl are each independently optionally substituted with a group selected from the group consisting of halogen, hydroxyl, nitro, cyano, C1-C3 alkyl, C1-C3 deuterated alkyl, C1-C3 haloalkyl, C1-C3 alkoxy, and C1-C3 haloalkoxy.

In one example, Y is -CH_2-, -CH_2CH_2-, -$CH(CH_2OCH_3)$-, -CH(CN)-, -CH(OH)-, -$CH(CH_3)$-, -$CH(CD_3)$-, -$C(CH_3)_2$-, -$CH(CF_3)$-, -$CH(CHF_2)$-, -$CH(CH_2F)$-, -$CH(CH_2CH_3)$-, -$CH(CH_2CH_2F)$-, -$CH(CH_2CF_2H)$-, -$CH(CH_2CF_3)$-, -$CH(CH_2CH_2CN)$-, -$CH(CH_2OH)$-, -$CH(CH_2CN)$-, -$CH(CH_2CH_2OH)$-, -CH(cyclopropyl)-, -CH(isopropyl)-, -$CH(CH_2CH_2CH_3)$-, -$CH(CH_2CH_2CH_2CH_3)$- or .

In one example, Y is -CH_2-.

In one example, Y is selected from the group consisting of: 

.

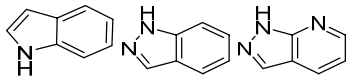
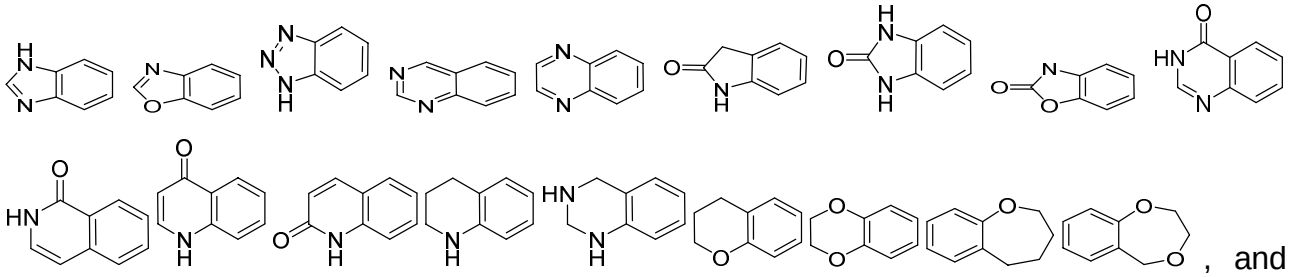
In one example, R^2 is H, cyano, halogen, C1-C3 alkyl, C1-C3 alkoxy, C1-C3 haloalkyl, C1-C3 haloalkoxy, C1-C3 deuterated alkoxy, $NR^{31}R^{32}$, C2-C4 alkynyl or CH_2OR^{33}, where R^{31} and R^{32} are each independently hydrogen or C1-C6 alkyl; or form, together with

the nitrogen atom to which they are attached, a 3- to 6-membered nitrogen-containing heterocyclyl; and R^{33} is hydrogen or C1-C6 alkyl.

In one example, R^2 is fluoro, chloro, hydroxyl, methoxy or cyano.

In one example, R^2 is hydrogen, fluoro, chloro, hydroxyl, methoxy or cyano.

In one example, ring A is phenyl, naphthalenyl, pyridinyl, pyrimidinyl, pyrazinyl, pyridazinyl, pyrrolyl, pyrazolyl, imidazolyl, 1,2,3,4-tetrahydronaphthalenyl, 2,3-dihydro-1H-indenyl, quinolinyl, isoquinolinyl, quinazolinyl, indolyl, indazolyl or benzo[d][1,3]dioxolanyl.

In one example, ring A is selected from the group consisting of   , and these groups can be attached to the rest of the molecule through any suitable ring atom.

In one example, R^1 is a substituent at any position on ring A; n1 is 0, 1, 2 or 3; and R^1 is each independently selected from C1-C3 alkyl, halogen, hydroxyl, C1-C3 alkoxy, C1-C3 haloalkyl, C1-C3 haloalkoxy, cyano, $NR^{21}R^{22}$, $C(O)NR^{23}R^{24}$, CH_2R^{25}, $N{=}S(O)(\text{C1-C3 alkyl})_2$, S(O)C1-C3 alkyl, $S(O)_2R^{26}$, -S-C1-C3 alkyl, C2-C4 alkenyl, C2-C4 alkynyl, C2-C4hydroxyl alkynyl, C1-C3cyano alkyl, triazolyl, -S-C1-C3 haloalkyl, C1-C3 hydroxylalkyl, $-CH_2C(O)NR^{27}R^{28}$, -C2-C4 alkynyl$NR^{29}R^{30}$, C2-C4 deuterated alkynyl, (C1-C3 alkoxy)C1-C3 haloalkyl- or cycloalkyl, in which the cycloalkyl is optionally substituted with halo or C1-C3 alkyl, where

R^{21} is H, C1-C3 alkyl, C1-C3 haloalkyl, C(O)C1-C3 alkyl or C(O)OC1-C3 alkyl; R^{22} is H, C1-C3 alkyl or C1-C3 haloalkyl; or R^{21} and R^{22}, together with the nitrogen atom to which they are attached, form a 3- to 6-membered nitrogen-containing heterocyclic group, where the 3- to 6-membered nitrogen-containing heterocyclic group is optionally substituted with 1 or 2 groups selected from halogen, methyl, trifluoromethyl, methoxy and trifluoromethoxy;

R^{23} and R^{24} are each independently H, C1-C3 alkyl, or C1-C3 haloalkyl; or R^{23} and R^{24}, together with the nitrogen atom to which they are attached, form a 3- to 6-membered nitrogen-containing heterocyclic group, where the 3- to 6-membered nitrogen-containing heterocyclic group is optionally substituted with 1 or 2 groups selected from halogen, methyl, trifluoromethyl, methoxy, and trifluoromethoxy;

R^{25} is hydroxyl, cyano, heterocyclyl, $NR^{251}R^{252}$, $C(O)NR^{253}R^{254}$ or SO_2C1-C3 alkyl, where R^{251}, R^{252}, R^{253}, and R^{254} are each independently H or C1-C3 alkyl; R^{251} and R^{252}, together with the nitrogen atom to which they are attached, form a 3- to 6-membered nitrogen containing heterocyclic group, where the 3- to 6-membered nitrogen containing heterocyclic group is optionally substituted with 1 or 2 groups selected from halogen, methyl, trifluoromethyl, methoxy, and trifluoromethoxy; and R^{253} and R^{254}, together with the nitrogen atom to which they are attached, form a 3- to 6-membered nitrogen containing heterocyclic group, where the 3- to 6-membered nitrogen containing heterocyclic group is optionally substituted with 1 or 2 groups selected from halogen, methyl, trifluoromethyl, methoxy, and trifluoromethoxy;

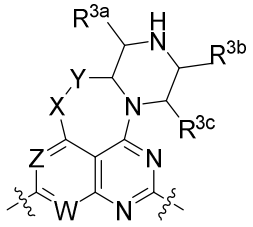
R^{26} is C1-C3 alkyl, C1-C3 haloalkyl, or $NR^{261}R^{262}$, where R^{261} and R^{262} are each independently H or C1-C3 alkyl, or R^{261} and R^{262}, together with the nitrogen atom to which they are attached, form a 3- to 6-membered nitrogen-containing heterocyclic group, where the 3- to 6-membered nitrogen-containing heterocyclic group is optionally substituted with 1 or 2 groups selected from halogen, methyl, trifluoromethyl, methoxy, and trifluoromethoxy;

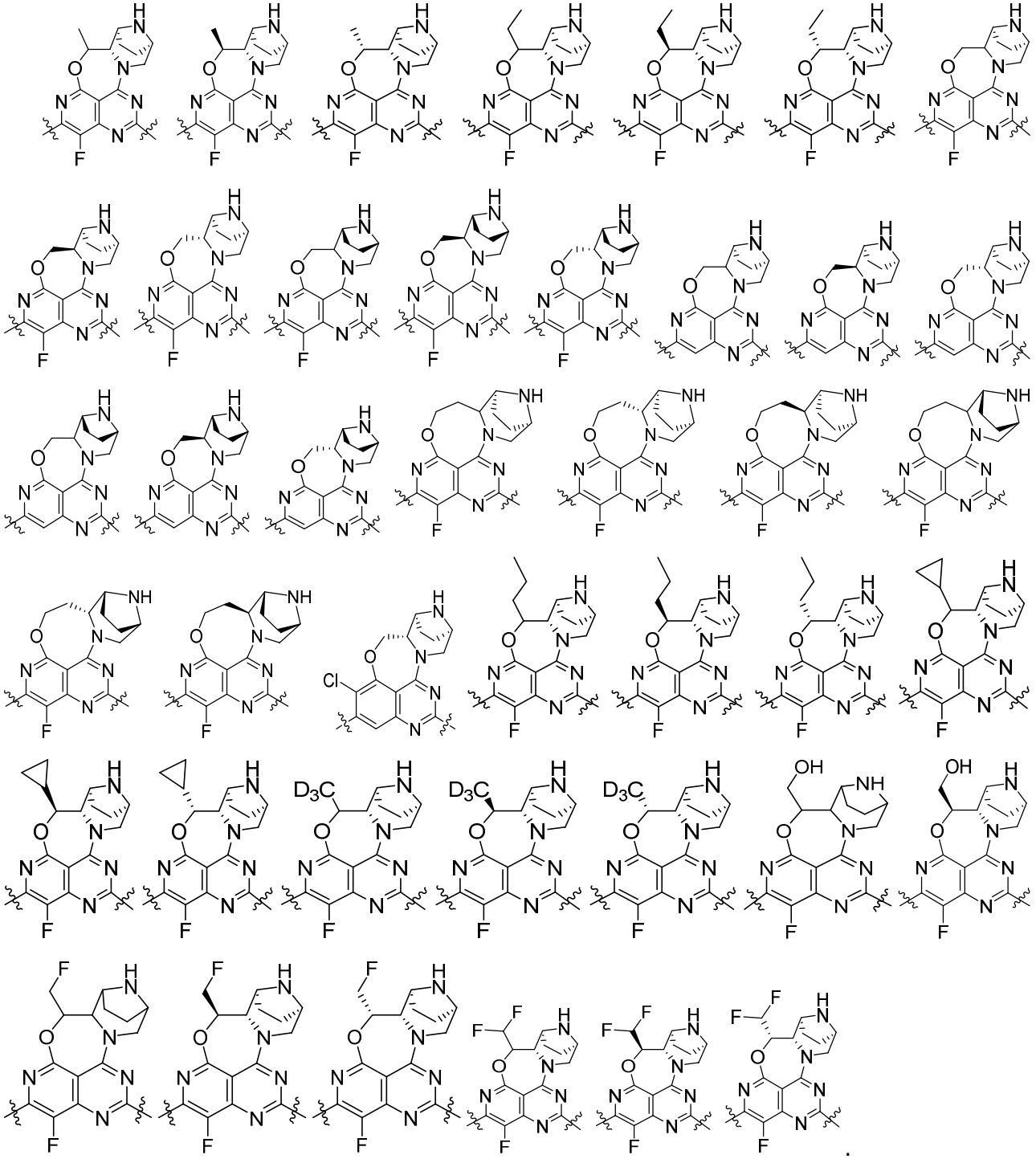
R^{27} and R^{28} are each independently H, C1-C3 alkyl, or C1-C3 haloalkyl; or R^{27} and R^{28}, together with the nitrogen atom to which they are attached, form a 3- to 6-membered nitrogen-containing heterocyclic group, where the 3- to 6-membered nitrogen-containing heterocyclic group is optionally substituted with 1 or 2 groups selected from halogen, methyl, trifluoromethyl, methoxy, and trifluoromethoxy;

R^{29} and R^{30} are each independently H, C1-C3 alkyl, or C1-C3 haloalkyl; or R^{29} and R^{30}, together with the nitrogen atom to which they are attached, form a 3- to 6-membered nitrogen-containing heterocyclic group, where the 3- to 6-membered nitrogen-containing heterocyclic group is optionally substituted with 1 or 2 groups selected from halogen, methyl, trifluoromethyl, methoxy, and trifluoromethoxy;

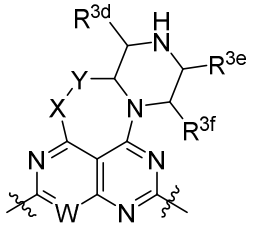
In one example, L_2 is methylene or ethylene or propylene, where 1 or 2 hydrogen atom(s) on any carbon atom(s) in the methylene or ethylene or propylene is/are optionally each independently substituted with deuterium or C1-C3 alkyl; or 2 hydrogen atoms on any carbon atom in the methylene or ethylene or propylene are optionally both replaced by -CH_2CH_2- or -$CH_2CH_2CH_2$-, to from cyclopropyl or cyclobutyl.

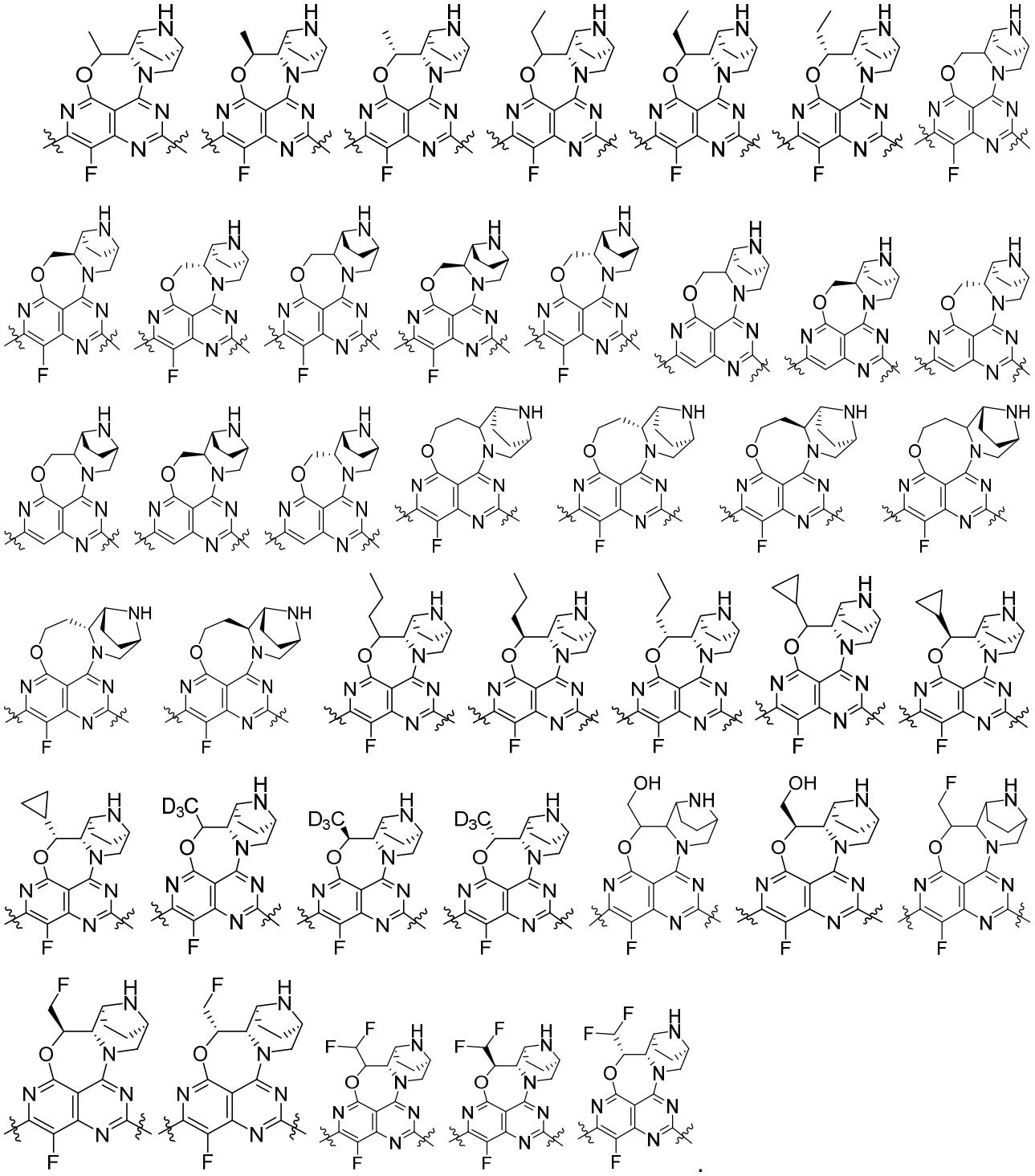
In one example, R^{3a}, R^{3b}, and R^{3c} are each independently hydrogen, fluoro, methyl or methoxy.

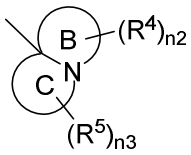
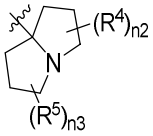
In one example,  is selected from the group consisting of:

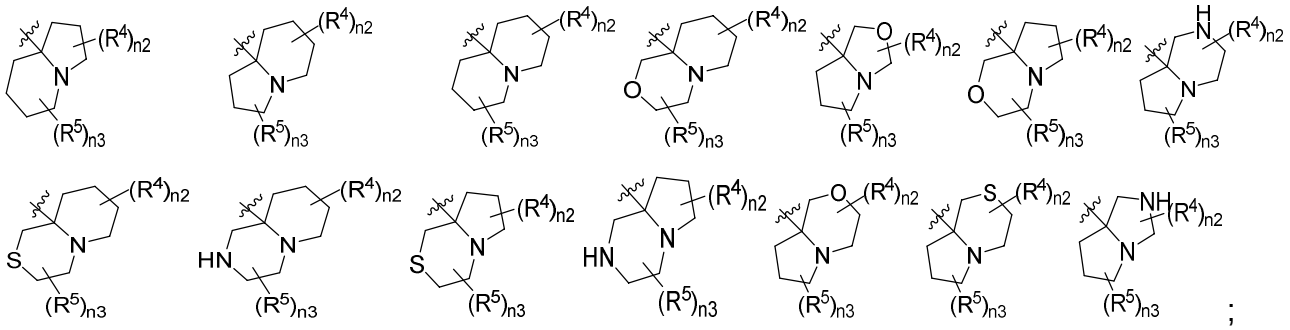


.

In one example,  is selected from the group consisting of:

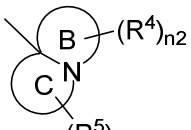


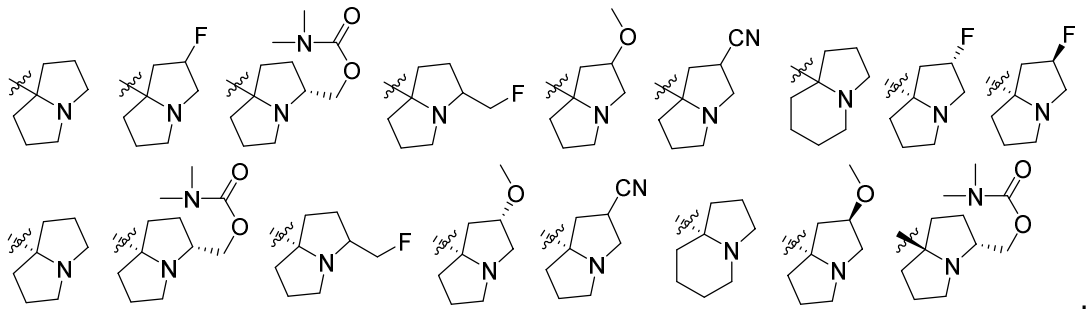
In one example,  is selected from the group consisting of: 



;

where in each formula, each R^4, R^5, n2, and n3 are each independently as defined in Formula (I).

In one example,  is selected from the group consisting of:



.

In one example, R^3 is hydrogen, fluoro, methyl or methoxy.

In one example, R^3 is hydrogen.

In one example, R^{3d}, R^{3e}, and R^{3f} are each independently hydrogen, fluoro, methyl or methoxy; or

R^{3d} and R^{3e} are linked to form -CHR^{3d1}- or -$CHR^{3d2}CHR^{3d3}$-; R^{3f} is hydrogen, fluoro, methyl or methoxy; and R^{3d1}, R^{3d2}, and R^{3d3} are each independently hydrogen, fluoro, methyl or methoxy; or

R^{3d} and R^{3f} are linked to form -CHR^{3f1}- or -$CHR^{3f2}CHR^{3f3}$-; R^{3e} is hydrogen, fluoro, methyl or methoxy; and R^{3f1}, R^{3f2}, and R^{3f3} are each independently hydrogen, fluoro, methyl or methoxy.

In one example, L is methylene or ethylene or propylene, where 1 or 2 hydrogen atom(s) on any carbon atom(s) in the methylene or ethylene or propylene is/are optionally each independently substituted with deuterium or C1-C3 alkyl; or 2 hydrogen atoms on any

carbon atom in the methylene or ethylene or propylene are optionally both replaced by -CH_2CH_2- or -$CH_2CH_2CH_2$-, to from cyclopropyl or cyclobutyl.

In one example, R^6 is hydrogen, -$N(R^{34})_2$, a 3- to 20-membered heterocyclyl, C1-C6 alkyl, -L-3- to 20-membered heterocyclyl, -L-C6-C14 aryl, -L-5- to 14-membered heteroaryl, -L-C3-C20 cycloalkyl, -L-$N(R^{34})_2$, -L-NHC(=NH)NH_2, -L-C(O)$N(R^{34})_2$, -L-C1-C6 haloalkyl, -L-OR^{34}, -L-$(CH_2OR^{34})(CH_2)_nOR^{34}$, -L-$NR^{34}$C(O)-C6-C14aryl, -L-COOH or -L-C(O)OC1-C6 alkyl, where the 3- to 20-membered heterocyclyl, the C6-C14aryl in the -L-NR^{34}C(O)-C6-C14 aryl, and the C3-C20 cycloalkyl are optionally substituted with one or more (for example, 1, 2, 3, 4 or 5) R^{35}, or optionally two hydrogen atoms on the same carbon atom are both replaced by -CH_2CH_2- or -$CH_2CH_2CH_2$- to form cyclopropyl or cyclobutyl; the C6-C14 aryl in the -L-C6-C14 aryl or the 5- to 14-membered heteroaryl in the -L-5- to 14-membered heteroaryl are optionally substituted with one or more (for example, 1, 2, 3, 4 or 5) R^{36}; and each L, each R^{34}, each R^{35}, and each R^{36} are each as defined above.

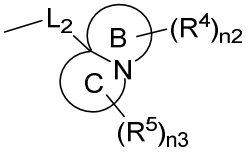
In one example, R^6 is hydrogen, -$N(R^{34})_2$, a 3- to 8-membered monocyclic heterocyclyl, a 5- to 20-membered spiro heterocyclyl, a 5- to 20-membered fused heterocyclyl, a 5- to 20-membered bridged heterocyclyl, C1-C6 alkyl, -L-3- to 8-membered monocyclic heterocyclyl, -L-5- to 20-membered spiro heterocyclyl, -L-5- to 20-membered fused heterocyclyl, -L-5- to 20-membered bridged heterocyclyl, -L-phenyl, -L-naphthalenyl, -L-5- to 14-membered heteroaryl, -L-C3-C12 cycloalkyl, -L-C5-C20 spiro cycloalkyl, C5-C20 fused cycloalkyl, -L-C5-C20 bridged cloalkyl, -L-$N(R^{34})_2$, -L-NHC(=NH)NH_2, -L-C(O)$N(R^{34})_2$, -L-C1-C6 haloalkyl, -L-OR^{34}, -L-$(CH_2OR^{34})(CH_2)_nOR^{34}$, -L-$NR^{34}$C(O)-phenyl, -L-$NR^{34}$C(O)-naphthalenyl, -L-COOH or -L-C(O)OC1-C6 alkyl, where the 3- to 8-membered monocyclic heterocyclyl, 5- to 20-membered spiro heterocyclyl, 5- to 20-membered fused heterocyclyl, 5- to 20-membered bridged heterocyclyl, C3-C12 cycloalkyl, C5-C20 spiro cycloalkyl, C5-C20 fused cycloalkyl, C5-C20 bridged cycloalkyl, the phenyl in the -L-NR^{34}C(O)-phenyl, and the naphthalenyl in the -L-NR^{34}C(O)-naphthalenyl are optionally substituted with one or more (for example, 1, 2, 3, 4 or 5) R^{35}, or optionally two hydrogen atoms on the same carbon atom are both replaced by -CH_2CH_2- or -$CH_2CH_2CH_2$- to form cyclopropyl or cyclobutyl; the phenyl in the -L-phenyl, the naphthalenyl in the -L-naphthalenyl, and the 5- to 14-membered heteroaryl in the -L-5- to 14-membered heteroaryl are optionally substituted with one or more (for example, 1, 2, 3, 4 or 5) R^{36}; and each L, each R^{34}, each R^{35}, and each R^{36} are each as defined above.

In one example, R^6 is hydrogen or -$N(R^{34})_2$. Preferably, each R^{34} is each independently hydrogen or C1-C3 alkyl; or 1 R^{34} is hydrogen and the other R^{34} is C1-C3 alkyl.

In one example, R^{34} is hydrogen, C1-C3 alkyl or C1-C3 cyanoalkyl.

In one example, C1-C6 alkyl is methyl, ethyl, isopropyl or isobutyl.

In one example, L is methylene or ethylene or propylene, where 1 or 2 hydrogen atom(s) on any carbon atom(s) in the methylene or ethylene or propylene is/are optionally each independently substituted with deuterium or C1-C3 alkyl; or 2 hydrogen atoms on any carbon atom in the methylene or ethylene or propylene are optionally both replaced by -CH_2CH_2- or -$CH_2CH_2CH_2$-, to from cyclopropyl or cyclobutyl.

In one example, R^6 is each independently 

; and R^4, R^5, L_2, ring B, ring C, n2, and n3 are as defined for various groups in Formula (I).

In one example, the heterocyclyl in R^6 is each independently hexahydro-1H-pyrrolizinyl, hexahydro-3H-pyrrolizin-3-one, hexahydro-1H-pyrrolo[2,1-c][1,4]oxazinyl, octahydroindolizinyl, hexahydropyrrolizin4(1H)-oxide, azetidinyl, pyrrolidinyl, pyrrolidin-2-one , oxacyclobutyl, piperidinyl, 1-azadicyclo[2.2.1]heptyl, morpholinyl, oxa-5-azadicyclo[2.2.1]hept-5-yl, thiopyranyl, 6-oxa-2-azaspiro [3.4]octyl, 7-oxa-2-azaspiro [3.5]nonyl, 2′,3′-dihydrospiro [cyclopropane-1,1’-indenyl], (2S)-1-azadicyclo[2.2.1]hept-2-yl or tetrahydrofuranyl. The above groups are each indpendently optionally substituted with one or more (for example, 1, 2, 3, 4 or 5) R^{35}, or optionally two hydrogen atoms on the same carbon atom are both replaced by -CH_2CH_2- or -$CH_2CH_2CH_2$- to form cyclopropyl or cyclobutyl; and each R^{35} is as defined above.

In one example, R^6 is -L-heterocyclyl; and the heterocyclyl is hexahydro-1H-pyrrolizinyl.

In one example, R^6 is -L-heterocyclyl; the heterocyclyl is a hexahydro-1H-pyrrolizinyl substituted with one R^{35} or a hexahydro-1H-pyrrolizinyl in which two hydrogen atoms on the same carbon atom are both replaced by -CH_2CH_2- or -$CH_2CH_2CH_2$- to form cyclopropyl or cyclobutyl, in which R^{35} is halogen, hydroxyl, C1-C3 hydroxylalkyl, C1-C3 haloalkyl, C1-C3 alkyl, C1-C3 alkoxy, phenyl, pyrazolyl or -$CH_2OC(O)N(R^{34})_2$.

In one example, the halo is fluoro.

In one example, the heterocyclyl is a hexahydro-1H-pyrrolizinyl that is further substituted with two additional R^{35}; and the two additional R^{35} are each independently C1-C3 alkyl.

In one example, R^6 is -L-heterocyclyl; the heterocyclyl is an azetidinyl substituted with one R^{35}, or an azetidinyl in which two hydrogen atoms on the same carbon atom are

both replaced by -CH_2CH_2- or -$CH_2CH_2CH_2$- to form cyclopropyl or cyclobutyl; and R^{35} is C1-C3 alkyl.

In one example, R^6 is -L-heterocyclyl; the heterocyclyl is a pyrrolidinyl substituted with one R^{35}, or pyrrolidinyl in which two hydrogen atoms on the same carbon atom are both replaced by -CH_2CH_2- or -$CH_2CH_2CH_2$- to form cyclopropyl or cyclobutyl, where R^{35} is hydroxylalkyl, haloalkyl, C1-C3 alkyl, alkoxy, aryl-C1-C3 alkyl, -phenyl, -O-phenyl, and -NHC(O)phenyl; in which the aryl in the aryl-C1-C3 alkyl, the phenyl, the phenyl in the -O-phenyl, or the phenyl in the -NHC(O)phenyl is each independently optionally substituted with one or more (for example, 1, 2, 3, 4 or 5) R^{36}.

In one example, the phenyl, or the phenyl in the -O-phenyl or -NHC(O)phenyl is substituted with -SO_2F.

In one example, R^6 is -L-heterocyclyl; and the heterocyclyl is a pyrrolidinyl substituted with two R^{35}, in which one R^{35} is C1-C3 alkyl, and the other R^{35} is C1-C3 alkoxy or halo.

In one example, R^6 is -L-heterocyclyl; and the heterocyclyl is pyrrolidin-2-one substituted with one R^{35} or pyrrolidin-2-one in which two hydrogen atoms on the same carbon atom are both replaced by -CH_2CH_2- or -$CH_2CH_2CH_2$- to form cyclopropyl or cyclobutyl, where R^{35} is C1-C3 alkyl.

In one example, R^6 is -L-heterocyclyl; the heterocyclyl is a piperidinyl substituted with one R^{35} or a piperidinyl in which two hydrogen atoms on the same carbon atom are both replaced by -CH_2CH_2- or -$CH_2CH_2CH_2$- to form cyclopropyl or cyclobutyl, where R^{35} is acetyl, (C1-C3 alkoxy)C1-C3 alkoxy or -C(O)CH_2Cl.

In one example, R^6 is -L-heterocyclyl; and the heterocyclyl is morpholinyl or oxa-5-azadicyclo[2.2.1]hept-5-yl.

In one example, R^6 is -L-heteroaryl; and the heteroaryl is optionally substituted with one or more R^{36}.

In one example, R^6 is -L-heteroaryl; L is methylene or ethylene or propylene, where 1 or 2 hydrogen atom(s) on any carbon atom(s) in the methylene or ethylene or propylene is/are optionally each independently substituted with deuterium or C1-C3 alkyl; or 2 hydrogen atoms on any carbon atom in the methylene or ethylene or propylene are optionally both replaced by -CH_2CH_2- or -$CH_2CH_2CH_2$- to form cyclopropyl or cyclobutyl; the heteroaryl is pyridinyl, pyrazolyl, imidazolyl, triazolyl, 4,5,6,7-tetrahydro-1H-indazolyl, benzoimidazolyl, imidazo[1, 2-a]pyridinyl or pyrimidinyl; and the above groups are each optionally substituted with one or more R^{36}.

In one example, R^6 is -L-heteroaryl; L is methylene or ethylene or propylene, where 1 or 2 hydrogen atom(s) on any carbon atom(s) in the methylene or ethylene or propylene

is/are optionally each independently substituted with deuterium or C1-C3 alkyl; or 2 hydrogen atoms on any carbon atom in the methylene or ethylene or propylene are optionally both replaced by $-CH_2CH_2-$ or $-CH_2CH_2CH_2-$ to form cyclopropyl or cyclobutyl; and the heteroaryl is substituted with one R^{36} substituted pyridinyl, where R^{36} is halogen, C1-C4 alkyl, $-N(R^5)_2$ or C1-C4 alkoxy.

In one example, R^6 is -L-heteroaryl; L is methylene or ethylene or propylene, where 1 or 2 hydrogen atom(s) on any carbon atom(s) in the methylene or ethylene or propylene is/are optionally each independently substituted with deuterium or C1-C3 alkyl; or 2 hydrogen atoms on any carbon atom in the methylene or ethylene or propylene are optionally both replaced by $-CH_2CH_2-$ or $-CH_2CH_2CH_2-$ to form cyclopropyl or cyclobutyl; and the heteroaryl is substituted with one R^{36} substituted pyrazolyl, where R^{36} is C1-C4 alkyl or $-N(R^{34})_2$.

In one example, R^6 is -L-heteroaryl; L is methylene or ethylene or propylene, where 1 or 2 hydrogen atom(s) on any carbon atom(s) in the methylene or ethylene or propylene is/are optionally each independently substituted with deuterium or C1-C3 alkyl; or 2 hydrogen atoms on any carbon atom in the methylene or ethylene or propylene are optionally both replaced by $-CH_2CH_2-$ or $-CH_2CH_2CH_2-$ to form cyclopropyl or cyclobutyl; and the heteroaryl is substituted with one R^{36} substituted imidazolyl, where R^{36} is C1-C4 alkyl, C1-C4 haloalkyl or C1-C4 hydroxylalkyl.

In one example, R^6 is -L-heteroaryl; L is methylene or ethylene or propylene, where 1 or 2 hydrogen atom(s) on any carbon atom(s) in the methylene or ethylene or propylene is/are optionally each independently substituted with deuterium or C1-C3 alkyl; or 2 hydrogen atoms on any carbon atom in the methylene or ethylene or propylene are optionally both replaced by $-CH_2CH_2-$ or $-CH_2CH_2CH_2-$ to form cyclopropyl or cyclobutyl; and the heteroaryl is substituted with one R^{36} substituted triazolyl, where R^{36} is C1-C4 alkyl.

In one example, R^6 is -L-aryl; and the aryl is optionally substituted with one or more R^{36}.

In one example, R^6 is -L- cycloalkyl; the cycloalkyl is optionally substituted with one or more R^{35}, or optionally two hydrogen atoms on the same carbon atom are both replaced by $-CH_2CH_2-$ or $-CH_2CH_2CH_2-$ to form cyclopropyl or cyclobutyl; and R^{35} is each as defined above.

In one example, R^6 is -L-$N(R^{34})_2$, where L is C1-C4 alkylene, in which 1 or 2 hydrogen atom(s) on any carbon atom(s) in the C1-C4 alkylene is/are optionally each independently substituted with deuterium or C1-C3 alkyl; or 2 hydrogen atoms on any carbon atom in the

C1-C4 alkylene are optionally both replaced by $-CH_2CH_2-$ or $-CH_2CH_2CH_2-$ to form cyclopropyl or cyclobutyl.

In one example, R^6 is $-L-N(R^{34})_2$, where L is methylene, ethylene or propylene, in which 1 or 2 hydrogen atom(s) on any carbon atom(s) in the methylene, ethylene or propylene is/are optionally each independently substituted with deuterium or C1-C3 alkyl; or 2 hydrogen atoms on any carbon atom in the methylene, ethylene or propylene are optionally both replaced by $-CH_2CH_2-$ or $-CH_2CH_2CH_2-$ to form cyclopropyl or cyclobutyl; and each R^{34} is independently selected from C1-C3 alkyl.

In one example, R^6 is $-L-NC(=NH)-NH_2$, where L is C1-C4 alkylene, in which 1 or 2 hydrogen atom(s) on any carbon atom(s) in the C1-C4 alkylene is/are optionally each independently substituted with deuterium or C1-C3 alkyl; or 2 hydrogen atoms on any carbon atom in the C1-C4 alkylene are optionally both replaced by $-CH_2CH_2-$ or $-CH_2CH_2CH_2-$ to form cyclopropyl or cyclobutyl.

In one example, L is ethylene or propylene.

In one example, R^6 is -L-C1-C6 haloalkyl, where L is C1-C4 alkylene, in which 1 or 2 hydrogen atom(s) on any carbon atom(s) in the C1-C4 alkylene is/are optionally each independently substituted with deuterium or C1-C3 alkyl; or 2 hydrogen atoms on any carbon atom in the C1-C4 alkylene are optionally both replaced by $-CH_2CH_2-$ or $-CH_2CH_2CH_2-$ to form cyclopropyl or cyclobutyl.

In one example, R^6 is $-L-OR^{34}$, where L is C1-C4 alkylene, where 1 or 2 hydrogen atom(s) on any carbon atom(s) in the C1-C4 alkylene is/are optionally each independently substituted with deuterium or C1-C3 alkyl; or 2 hydrogen atoms on any carbon atom in the C1-C4 alkylene are optionally both replaced by $-CH_2CH_2-$ or $-CH_2CH_2CH_2-$ to form cyclopropyl or cyclobutyl.

In one example, R^6 is $-L-(CH_2OR^{34})(CH_2)_nOR^{34}$, where L is C1-C4 alkylene, in which 1 or 2 hydrogen atom(s) on any carbon atom(s) in the C1-C4 alkylene is/are optionally each independently substituted with deuterium or C1-C3 alkyl; or 2 hydrogen atoms on any carbon atom in the C1-C4 alkylene are optionally both replaced by $-CH_2CH_2-$ or $-CH_2CH_2CH_2-$ to form cyclopropyl or cyclobutyl.

In one example, R^6 is $-L-NR^{34}C(O)$-aryl, where L is C1-C4 alkylene, in which 1 or 2 hydrogen atom(s) on any carbon atom(s) in the C1-C4 alkylene is/are optionally each independently substituted with deuterium or C1-C3 alkyl; or 2 hydrogen atoms on any carbon atom in the C1-C4 alkylene are optionally both replaced by $-CH_2CH_2-$ or $-CH_2CH_2CH_2-$ to form cyclopropyl or cyclobutyl.

In one example, R^6 is -L-heterocyclyl; L is C1-C4 alkylene, in which 2 hydrogen atoms on any carbon atom in the C1-C4 alkylene optionally each independently substituted with deuterium or C1-C6 alkyl; or 2 hydrogen atoms on any carbon atom in the C1-C4 alkylene are optionally both replaced by $-CH_2CH_2-$ or $-CH_2CH_2CH_2-$ to form cyclopropyl or cyclobutyl.

In one example, R^6 is -L-6- to 10-membered fused heterocyclyl; 2 hydrogen atoms on the same carbon atom in any 1 or 2 carbon atoms in the 6- to 10-membered fused heterocyclyl are optionally both replaced by $=CR^{2a}R^{2b}$; and/or the 6- to 10-membered fused heterocyclyl is optionally further substituted with 1 or more R^{6a}, where R^{2a} and R^{2b} are each independently hydrogen, halogen, cyano, C1-C4 alkyl or C1-C4 haloalkyl; and each R^{6a} is each independently halo.

In one example, L is methylene or ethylene or propylene, where 2 hydrogen atoms on any carbon atom in the methylene or ethylene or propylene are optionally each independently substituted with deuterium or C1-C3 alkyl; or 2 hydrogen atoms on any carbon atom in the methylene or ethylene or propylene are optionally both replaced by $-CH_2CH_2-$ or $-CH_2CH_2CH_2-$ to form cyclopropyl or cyclobutyl.

In one example, W is CR^{20}; and R^{20} is cyclopropyl, cyclopropyl-O-, cyclobutyl, cyclobutyl-O-, cyclopentyl, cyclopentyl-O-, tetrahydrofuranyl, tetrahydrofuran-O-, where the cyclopropyl, cyclobutyl, cyclopentyl, and tetrahydrofuranyl are each independently substituted with halo.

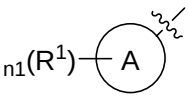
In one example, W is CR^{20}; and R^{20} is hydrogen, halogen, C1-C6 alkyl, C3-C6 cycloalkyl, C3-C6 cycloalkyl-O-, 3- to 6-membered heterocyclyl or 3- to 6-membered heterocyclyl-O-, where the C3-C6 cycloalkyl, and the 3- to 6-membered heterocyclyl are each independently substituted with halo.

In one example, R^{20} is halo or C1-C3 alkyl.

In one example, R^{20} is fluoro.

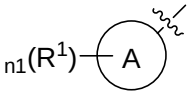
In one example, R^{20} is methyl.

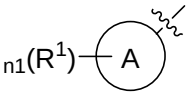
In one example, L_2 or L is methylene or ethylene or propylene, where 2 hydrogen atoms on any carbon atom in the methylene or ethylene or propylene are optionally each independently substituted with deuterium or C1-C3 alkyl; or 2 hydrogen atoms on any carbon atom in the methylene or ethylene or propylene are optionally both replaced by $-CH_2CH_2-$ or $-CH_2CH_2CH_2-$ to form cyclopropyl or cyclobutyl.

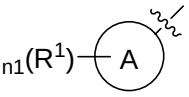
In one example, 

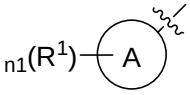
is phenyl substituted with one, two, three or four R^1, where each R^1 is independently halogen, hydroxyl, ethynyl, methyl, methyl-O-, methyl-S-,

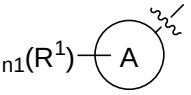
trifluoromethyl, trifluoromethyl-O-, amino, isopropyl, or cyclopropyl; and the cyclopropyl is optionally substituted with halo or methyl. Preferably, one R^1 is ethynyl, and the remaining R^1 is each independently halogen, hydroxyl, ethynyl, methyl, methyl-O-, methyl-S-, trifluoromethyl, trifluoromethyl-O-, amino, isopropyl or cyclopropyl; and the cyclopropyl is optionally substituted with halo or methyl.

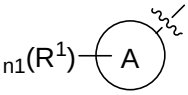
In one example,  is naphthalenyl substituted with one, two, three or four R^1, where R^1 is each independently halogen, hydroxyl, ethynyl, methyl, methyl-O-, methyl-S-, trifluoromethyl, trifluoromethyl-O-, amino, isopropyl, cyano or cyclopropyl; and the cyclopropyl is optionally substituted with halo or methyl. Preferably, one R^1 is ethynyl, and the remaining R^1 is each independently halogen, hydroxyl, ethynyl, methyl, methyl-O-, methyl-S-, trifluoromethyl, trifluoromethyl-O-, amino, isopropyl or cyclopropyl; and the cyclopropyl is optionally substituted with halo or methyl.

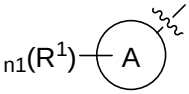
In one example,  is naphthalenyl substituted with one, two or three R^1, where each R^1 is each independently halogen, hydroxyl, ethynyl, methyl, ethyl, amino, cyano or difluoromethyl. Preferably, one R^1 is ethynyl, and the remaining R^1 is each independently halogen, hydroxyl, ethynyl, methyl, methyl-O-, methyl-S-, trifluoromethyl, trifluoromethyl-O-, amino, isopropyl or cyclopropyl; and the cyclopropyl is optionally substituted with halo or methyl.

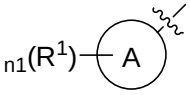
In one example,  is naphthalenyl substituted with one or two R^1, where each R^1 is each independently halogen, ethynyl, or amino.

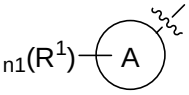
In one example,  is heteroaryl optionally substituted with one or more R^1.

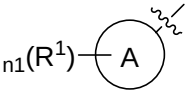
In one example,  is pyridinyl substituted with one, two, three or four R^1, where each R^1 is each independently halogen, hydroxyl, ethynyl, methyl, methyl-O-, methyl-S-, trifluoromethyl, trifluoromethyl-O-, amino, isopropyl, or cyclopropyl; and the cyclopropyl is optionally substituted with halo or methyl. Preferably, one R^1 is ethynyl, and the remaining R^1 is each independently halogen, hydroxyl, ethynyl, methyl, methyl-O-, methyl-S-, trifluoromethyl, trifluoromethyl-O-, amino, isopropyl or cyclopropyl; and the cyclopropyl is optionally substituted with halo or methyl.

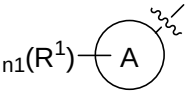
In one example,  is quinolinyl, isoquinolinyl, indazolyl or benzo[d][1,3]dioxolanyl optionally substituted with one or more (for example, 1, 2, 3, 4 or 5) R^1.

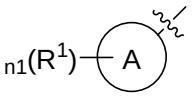
In one example,  is isoquinolinyl substituted with one, two, three or four R^1, where R^1 is each independently halogen, hydroxyl, ethynyl, methyl, methyl-O-, methyl-S-, trifluoromethyl, trifluoromethyl-O-, amino, isopropyl, or cyclopropyl; and the cyclopropyl is optionally substituted with halo or methyl. Preferably, one R^1 is ethynyl, and the remaining R^1 is each independently halogen, hydroxyl, ethynyl, methyl, methyl-O-, methyl-S-, trifluoromethyl, trifluoromethyl-O-, amino, isopropyl or cyclopropyl; and the cyclopropyl is optionally substituted with halo or methyl.

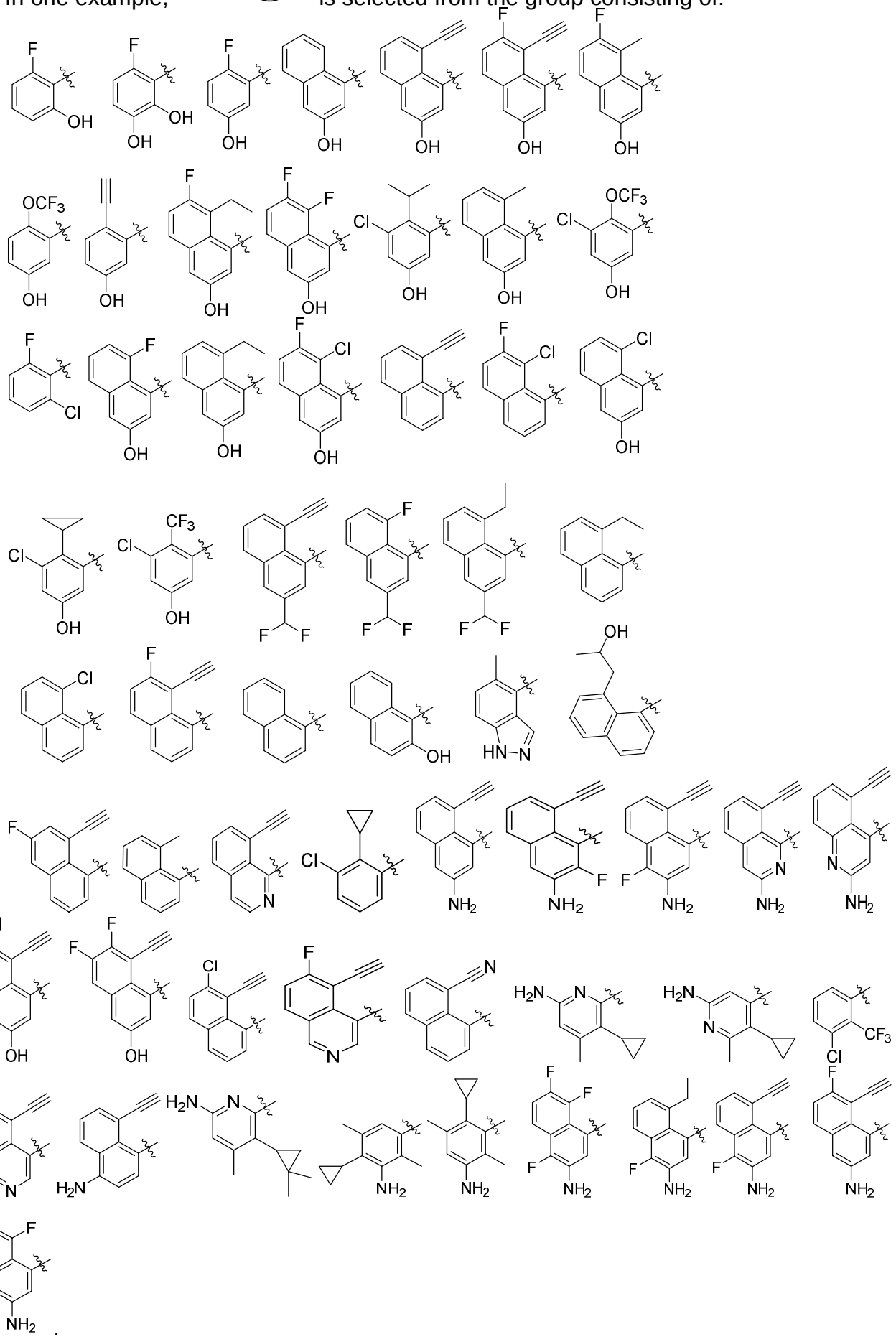
In one example,  is isoquinolinyl substituted with one, two or three R^1, where R^1 is each independently halogen, hydroxyl, ethynyl, methyl, methyl-O-, methyl-S-, trifluoromethyl, trifluoromethyl-O-, amino, isopropyl, or cyclopropyl; and the cyclopropyl is optionally substituted with halo or methyl. Preferably, one R^1 is ethynyl, and the remaining R^1 is each independently halogen, hydroxyl, ethynyl, methyl, methyl-O-, methyl-S-, trifluoromethyl, trifluoromethyl-O-, amino, isopropyl or cyclopropyl; and the cyclopropyl is optionally substituted with halo or methyl.

In one example,  is quinolinyl substituted with one, two, three or four R^1, where R^1 is each independently halogen, hydroxyl, ethynyl, methyl, methyl-O-, methyl-S-, trifluoromethyl, trifluoromethyl-O-, amino, isopropyl, or cyclopropyl; and the cyclopropyl is optionally substituted with halo or methyl. Preferably, one R^1 is ethynyl, and the remaining R^1 is each independently halogen, hydroxyl, ethynyl, methyl, methyl-O-, methyl-S-, trifluoromethyl, trifluoromethyl-O-, amino, isopropyl or cyclopropyl; and the cyclopropyl is optionally substituted with halo or methyl.

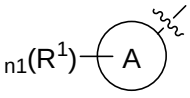
In one example,  is indazolyl substituted with one, two or three R^1, where R^1 is each independently C1-C3 alkyl.

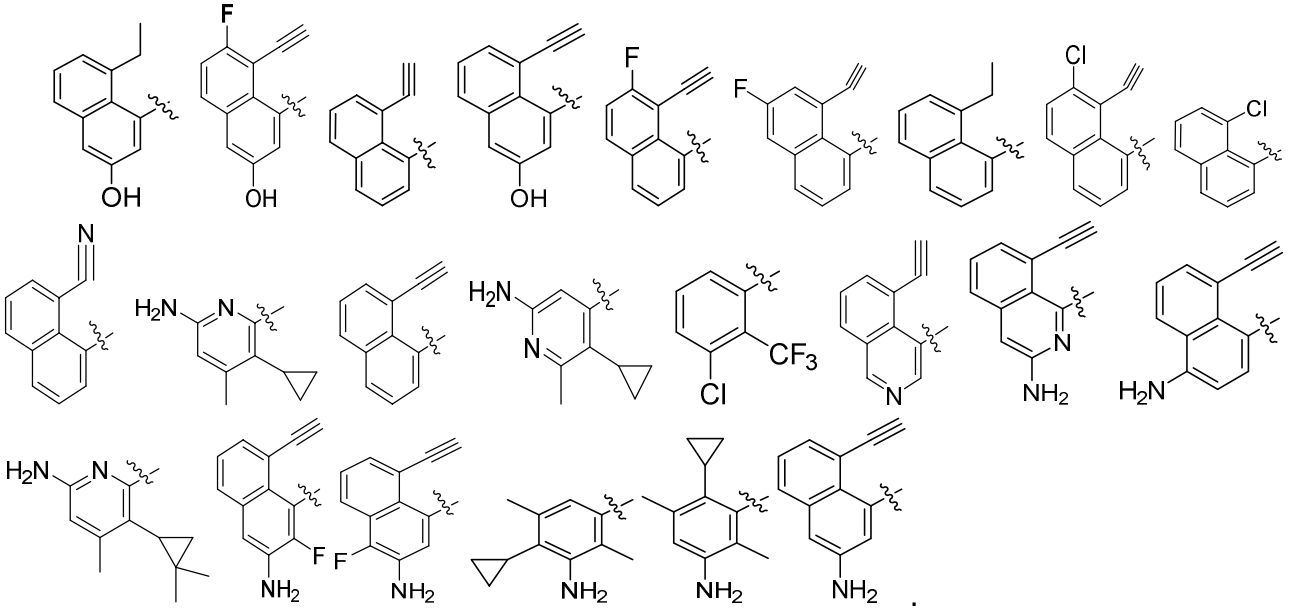
In one example,  is benzo[d][1, 3]dioxolanyl substituted with two R^1 where R^1 is each independently selected from halo.

In one example,  is selected from the group consisting of:

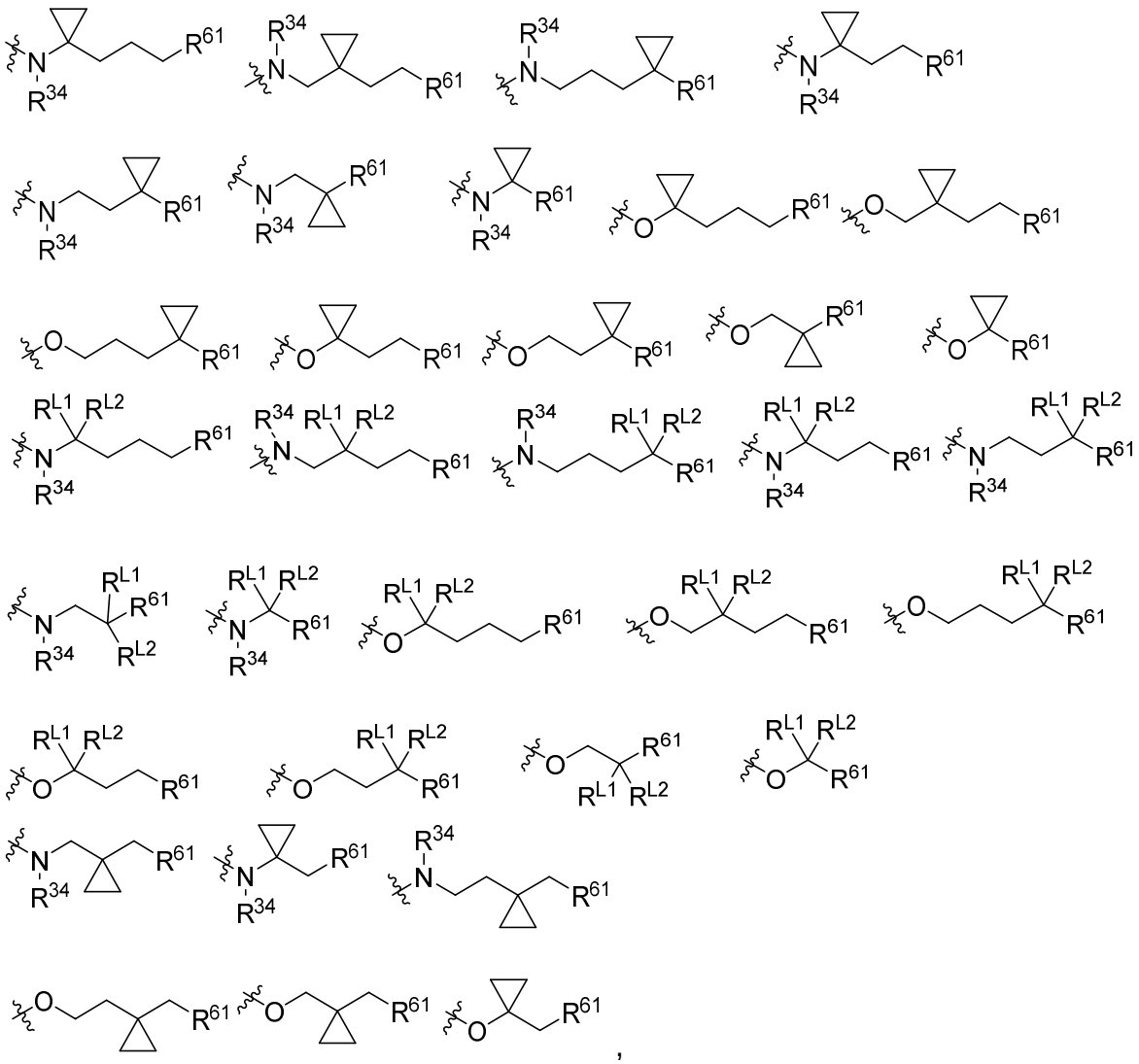


.

In one example,  is selected from the group consisting of:

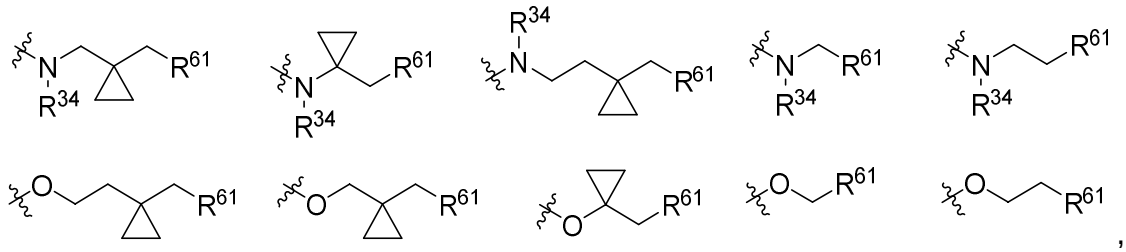


In one example, the -L_3-R^6 is selected from the group consisting of:



where in each formula, R^{L1} and R^{L2} are each independently hydrogen, deuterium, C1-C6 alkyl or C1-C6 haloalkyl; R^{61} is heterocyclyl, aryl, heteroaryl, cycloalkyl, $-N(R^{34})_2$, $-NHC(=NH)NH_2$, $-C(O)N(R^{34})_2$, -C1-C6 haloalkyl, $-OR^{34}$, $-(CH_2OR^{34})(CH_2)_nOR^{34}$, $-NR^{34}C(O)$-aryl, -COOH or -C(O)OC1-C6 alkyl, where the heterocyclyl, the aryl in the $-NR^{34}C(O)$-aryl, and the cycloalkyl are each optionally substituted with one or more (for example, 1, 2, 3, 4 or 5) R^{35}, or optionally two hydrogen atoms on the same carbon atom are both replaced by $-CH_2CH_2-$ or $-CH_2CH_2CH_2-$ to form cyclopropyl or cyclobutyl; the aryl and the heteroaryl are each optionally substituted with one or more (for example, 1, 2, 3, 4 or 5) R^{36}; and each R^{34}, each R^{35}, and each R^{36} are each as defined above. Preferably, in each formula, R^{34} in $N-R^{34}$ is H.

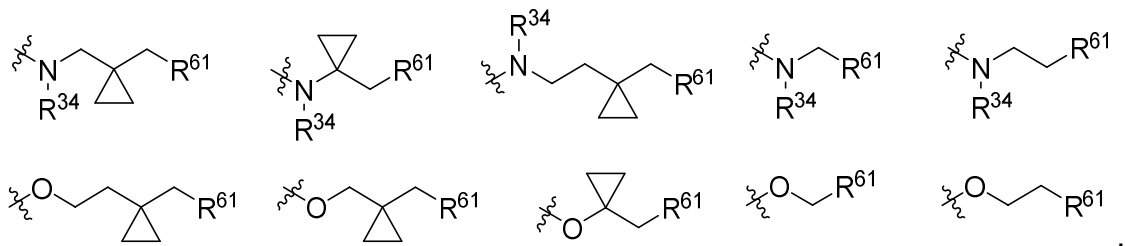
In one example, the $-L_3-R^6$ is selected from the group consisting of:



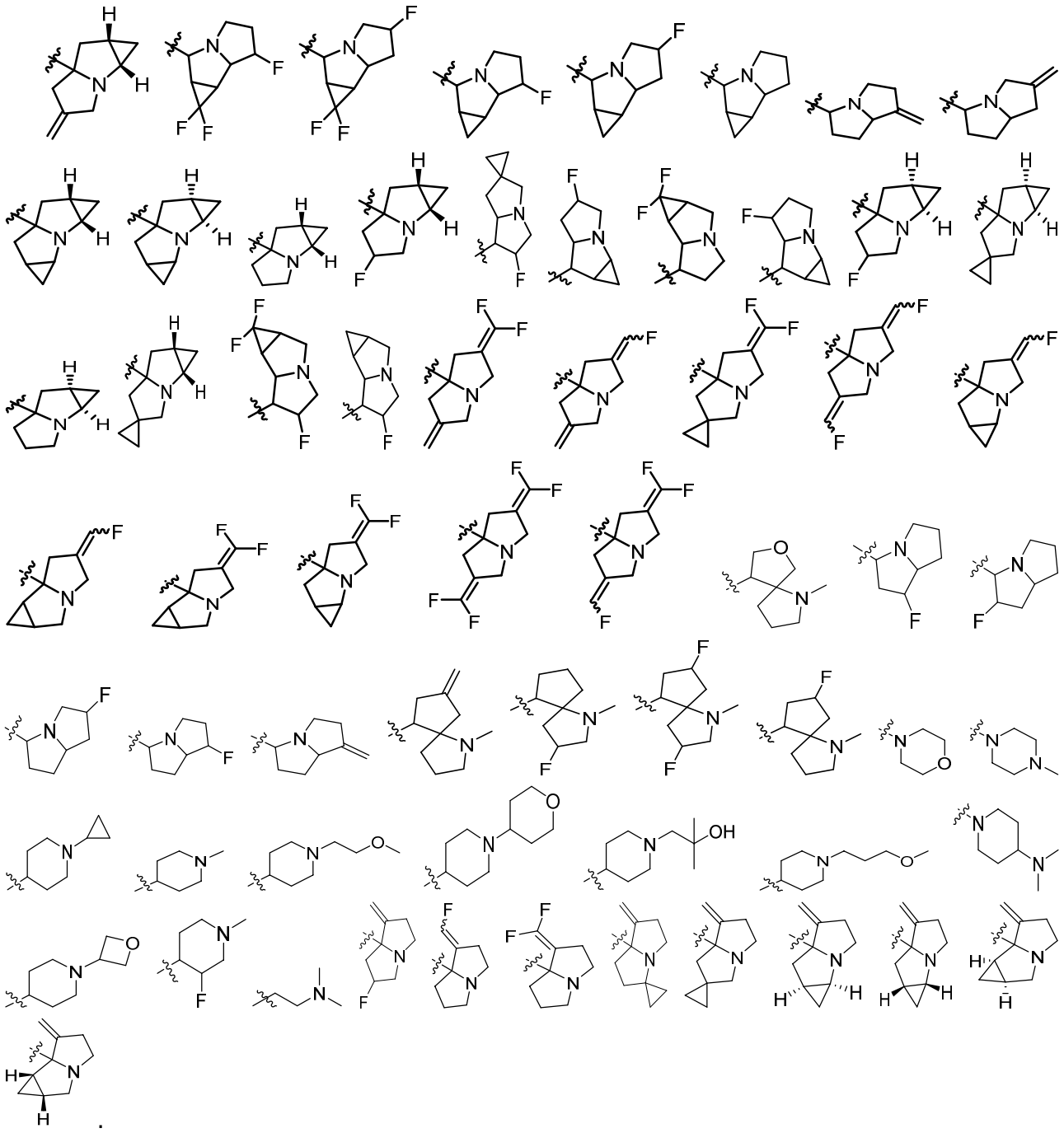
,

where in each formula, R^{61} is heterocyclyl, aryl, heteroaryl, cycloalkyl, $-N(R^{34})_2$, $-NHC(=NH)NH_2$, $-C(O)N(R^{34})_2$, -C1-C6 haloalkyl, $-OR^{34}$, $-(CH_2OR^{34})(CH_2)_nOR^{34}$, $-NR^{34}C(O)$-aryl, -COOH or -C(O)OC1-C6 alkyl, where the heterocyclyl needs to be substituted with one or more (for example, 1, 2, 3, 4 or 5) R^{35}, or optionally two hydrogen atoms on the same carbon atom are both replaced by $-CH_2CH_2-$ or $-CH_2CH_2CH_2-$ to form cyclopropyl or cyclobutyl; the aryl in $-NR^{34}C(O)$-aryl and the cycloalkyl are each optionally substituted with one or more (for example, 1, 2, 3, 4 or 5) R^{35}, or optionally two hydrogen atoms on the same carbon atom are both replaced by $-CH_2CH_2-$ or $-CH_2CH_2CH_2-$ to form cyclopropyl or cyclobutyl; the aryl and the heteroaryl are each optionally substituted with one or more (for example, 1, 2, 3, 4 or 5) R^{36}; and each R^{34}, each R^{35}, and each R^{36} are each as defined above. Preferably, in each formula, R^{34} in $N-R^{34}$ is H.

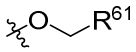
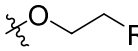
In one example, the $-L_3-R^6$ is $-NH-R^{61}$, $-OR^{61}$ or $-R^{61}$; or the $-L_3-R^6$ is selected from the group consisting of:



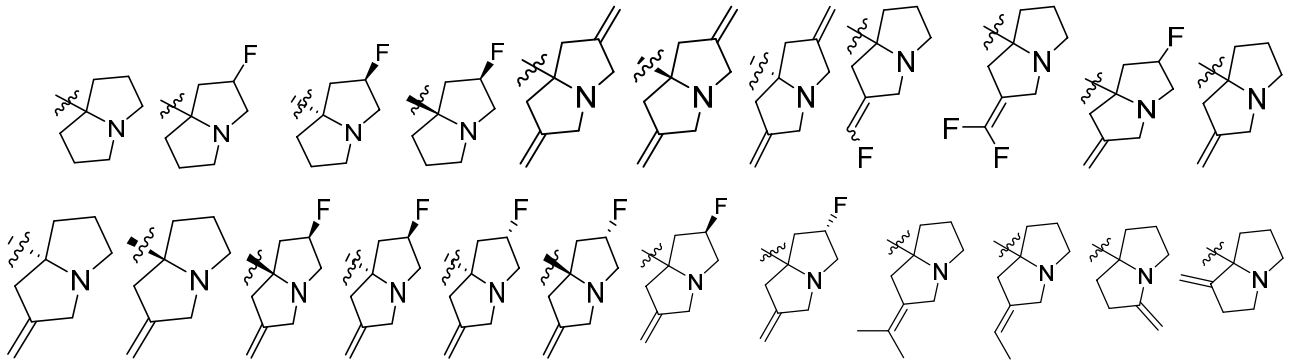
,

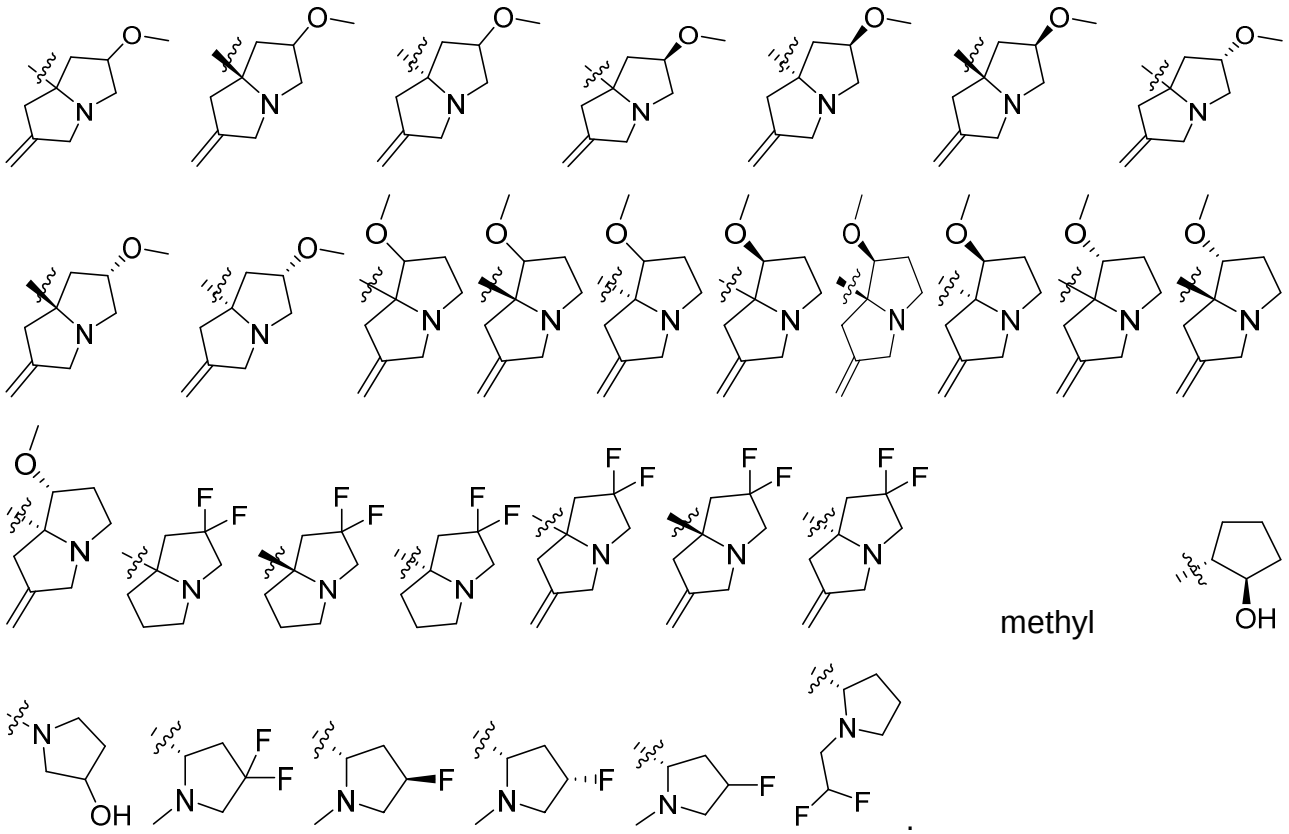


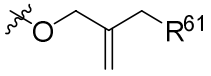
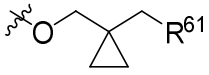
.

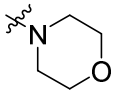
In one example, the -L_3-R^6 is -O-R^{61},  or .

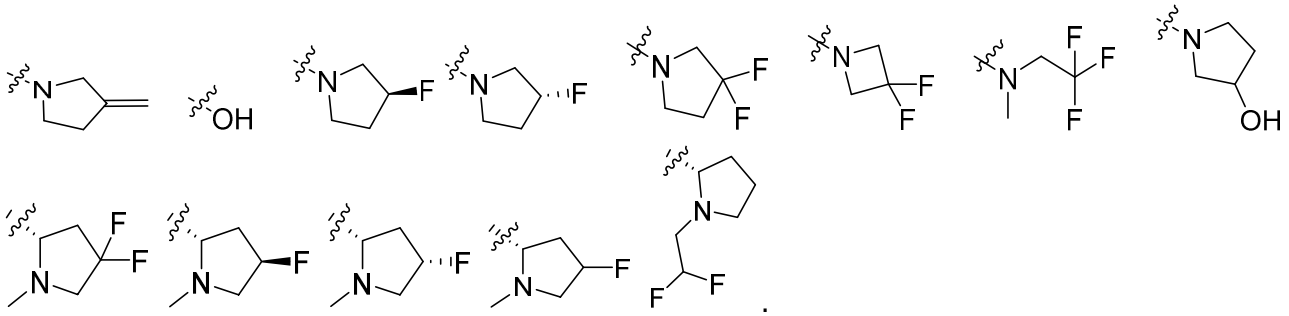
In one example, R^{61} is independently selected from the group consisting of:





In one example, the -L_3-R^6 is  or . In one example, R^{61} is -OR^{34}, -$N(R^{34})_2$ or heterocyclyl, where the heterocyclyl is optionally substituted with one or more (for example, 1, 2, 3, 4 or 5) R^{35}, or optionally two hydrogen atoms on the same carbon atom are both replaced by -CH_2CH_2- or -$CH_2CH_2CH_2$- to form cyclopropyl or cyclobutyl; and each R^{34} and each R^{35} are each as defined above. Preferably, R^{35} is each independently halogen, hydroxyl, C1-C3 alkyl, C2-C4 alkenylene, C2-C4 halo alkenylene or C1-C3 haloalkyl. preferably, R^{34} is each independently hydrogen, C1-C3 alkyl or C1-C3 haloalkyl.

In one example, R^{61} is independently selected from the group consisting of: 

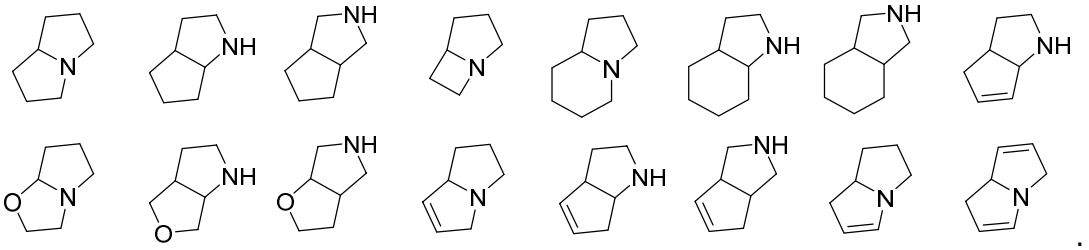


In one example, R^{61} is hexahydro-1H-pyrrolizinyl.

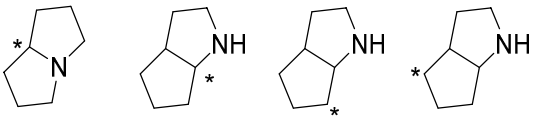
In one example, R^{61} is hexahydro-1H-pyrrolizinyl substituted with one R^{35}, where R^{35} is halogen, hydroxyl, C1-C3 hydroxylalkyl, C1-C3 haloalkyl, C1-C3 alkyl, C1-C3 alkoxy, C2-C3 alkenyl, C2-C3 haloalkenyl, phenyl, pyrazolyl or -$CH_2OC(O)N(R^{34})_2$; R^{34} is each independently hydrogen, C1-C3 alkyl or C1-C3 haloalkyl; or two R^{34}, together with the

nitrogen atom to which they are attached, form a 3- to 6-membered nitrogen containing heterocyclic group, where the 3- to 6-membered nitrogen containing heterocyclic group is optionally substituted with 1 or 2 groups selected from halogen, methyl, trifluoromethyl, methoxy, and trifluoromethoxy.

In one example, the 6- to 10-membered fused heterocyclic group is selected from the group consisting of:

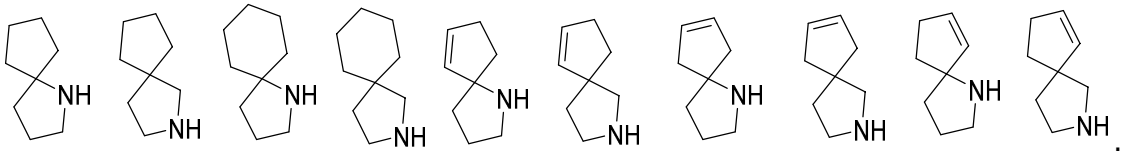


In one example, the 6- to 10-membered fused heterocyclic group is selected from the group consisting of:

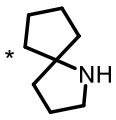


, where the carbon atom marked with * is a carbon atom attached to the rest of the molecule.

In one example, the 7- to 11-membered spiro heterocyclyl is selected from the group consisting of:

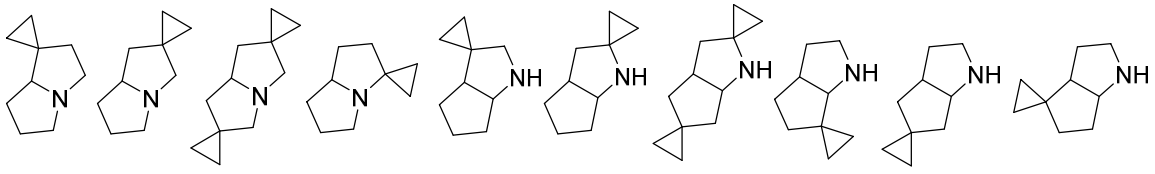


In one example, the 7- to 11-membered spiro heterocyclyl is selected from the group consisting of:

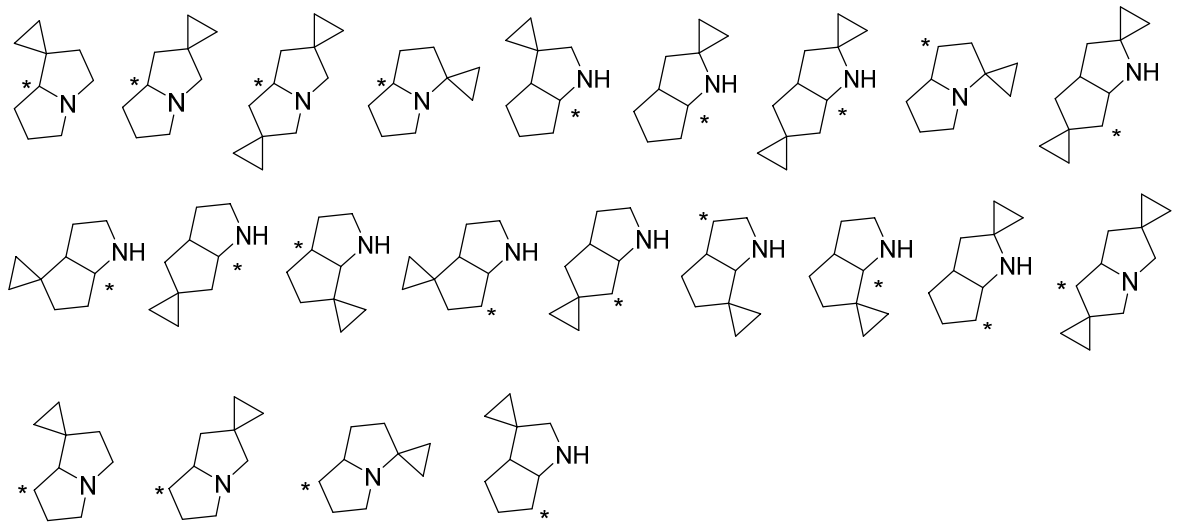


, where the carbon atom marked with * is a carbon atom attached to the rest of the molecule.

In one example, the sfpiro-substituted 6- to 10-membered fused heterocyclyl is selected from the group consisting of:

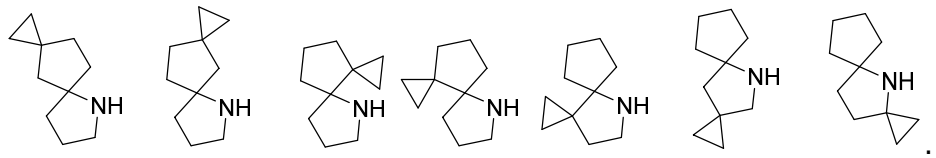


In one example, the sfpiro-substituted 6- to 10-membered fused heterocyclyl is selected from the group consisting of:

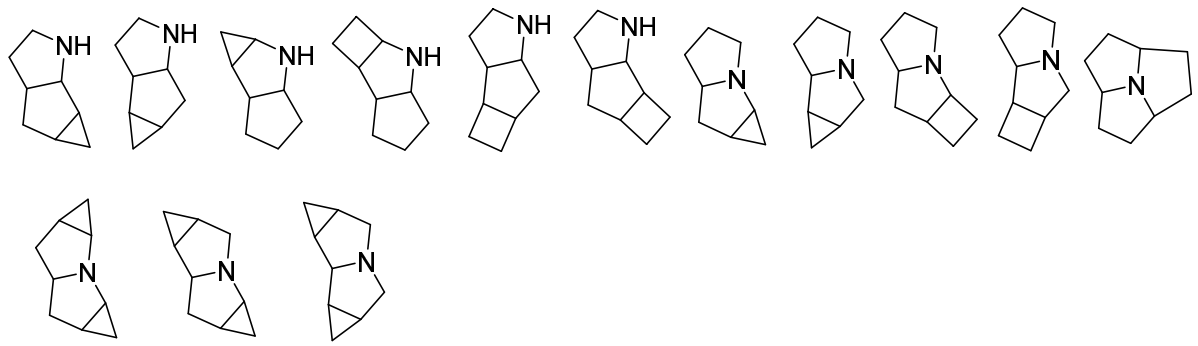


where the carbon atom marked with * is a carbon atom attached to the rest of the molecule.

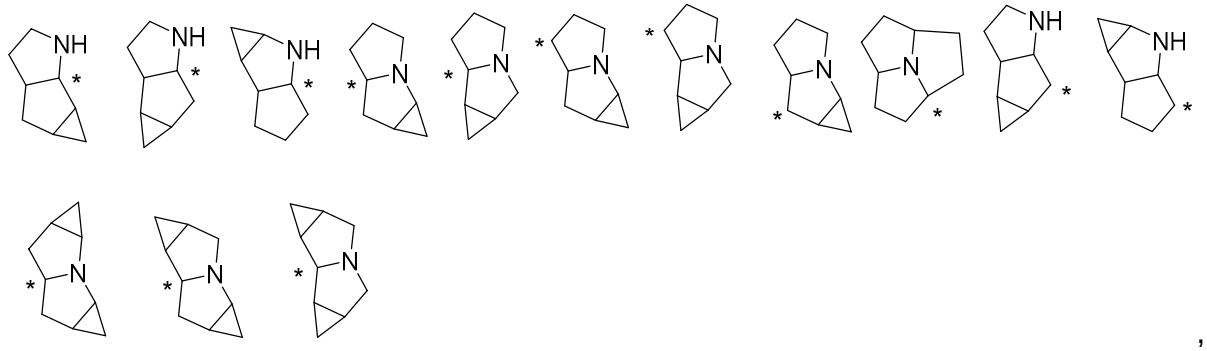
In one example, the spiro-substituted 7- to 11-membered spiro heterocyclyl is selected from the group consisting of:



In one example, the parallel-substituted 6- to 10-membered fused heterocyclyl is selected from the group consisting of:

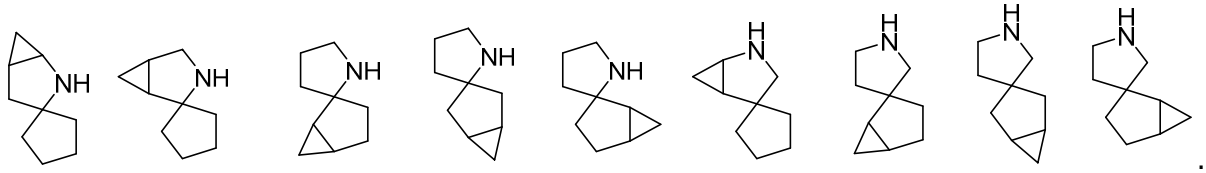


In one example, the parallel-substituted 6- to 10-membered fused heterocyclyl is selected from the group consisting of:



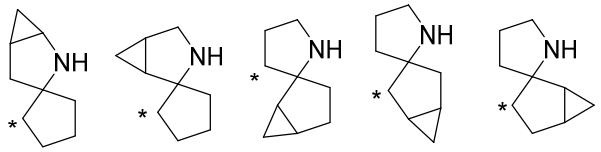
where the carbon atom marked with * is a carbon atom attached to the rest of the molecule.

In one example, the parallel-substituted 7- to 11-membered spiro heterocyclyl is selected from the group consisting of:



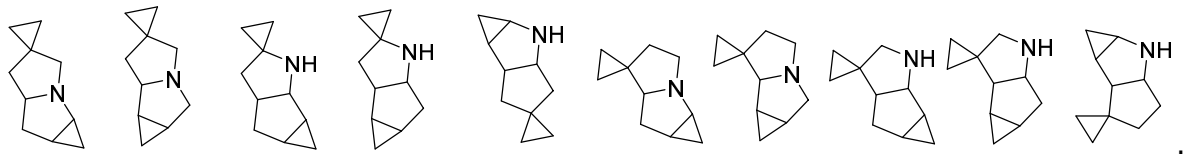
.

In one example, the parallel-substituted 7- to 11-membered spiro heterocyclyl is selected from the group consisting of:



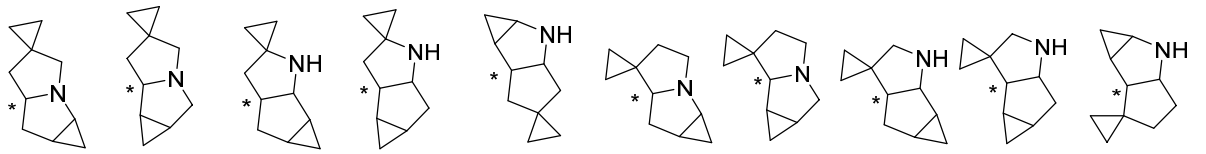
, where the carbon atom marked with * is a carbon atom attached to the rest of the molecule.

In one example, the spiro- and parallel- 6- to 10-membered fused heterocyclyl is selected from the group consisting of:



.

In one example, the spiro- and parallel- 6- to 10-membered fused heterocyclyl is selected from the group consisting of:



,

where the carbon atom marked with * is a carbon atom attached to the rest of the molecule.

In one example, L_3 is O; R^6 is -L-hexahydro-1H-pyrrolizinyl, where L is C1-C4 alkylene; and 2 hydrogen atoms on any 1 carbon atom in the hexahydro-1H-pyrrolizinyl are both replaced by $=CR^{2a}R^{2b}$, where R^{2a} and R^{2b} are each independently hydrogen, halogen, cyano, C1-C4 alkyl or C1-C4 haloalkyl. Preferably, the hexahydro-1H-pyrrolizinyl is further optionally substituted with 1 or more (for example, 1, 2, 3, 4 or 5) R^{6a}, where R^{6a} is each independently halogen, hydroxyl, C1-C6 hydroxylalkyl, C1-C6 alkyl, C2-C6 alkenyl, C2-C6 alkynyl, C1-C6 haloalkyl, C1-C6 alkoxy, C1-C6 haloalkoxy or cyano.

In one example, L_3 is O; R^6 is -L-hexahydro-1H-pyrrolizinyl, where L is C1-C4 alkylene; and 2 hydrogen atoms on any 1 carbon atom in the hexahydro-1H-pyrrolizinyl are both replaced by $=CR^{2a}R^{2b}$, where R^{2a} and R^{2b}, together with the carbon atom to which they

are attached, form a C3-C6 monocyclic cycloalkyl or a 3- to 6-membered monocyclic heterocyclyl; the C3-C6 monocyclic cycloalkyl or the 3- to 6-membered monocyclic heterocyclyl is optionally substituted with 1, 2, or 3 groups selected from halogen, cyano, C1-C4 alkyl, C1-C4 alkoxy, C1-C4 haloalkyl, C1-C4 haloalkoxy, C6-C10 aryl, or a 5- or 6-membered monocyclic heteroaryl. Preferably, the hexahydro-1H-pyrrolizinyl is further optionally substituted with 1 or more (for example, 1, 2, 3, 4 or 5) R^{6a}, where R^{6a} is each independently halogen, hydroxyl, C1-C6 hydroxylalkyl, C1-C6 alkyl, C2-C6 alkenyl, C2-C6 alkynyl, C1-C6 haloalkyl, C1-C6 alkoxy, C1-C6 haloalkoxy or cyano.

In one example, L_3 is O; R^6 is -L-hexahydro-1H-pyrrolizinyl, where L is C1-C4 alkylene; and 2 hydrogen atoms on one carbon atom in any 2 carbon atoms in the hexahydro-1H-pyrrolizinyl are both replaced by $=CR^{2a}R^{2b}$, where R^{2a} and R^{2b} are each independently hydrogen, halogen, cyano, C1-C4 alkyl or C1-C4 haloalkyl. Preferably, the hexahydro-1H-pyrrolizinyl is further optionally substituted with 1 or more (for example, 1, 2, 3, 4 or 5) R^{6a}, where R^{6a} is each independently halogen, hydroxyl, C1-C6 hydroxylalkyl, C1-C6 alkyl, C2-C6 alkenyl, C2-C6 alkynyl, C1-C6 haloalkyl, C1-C6 alkoxy, C1-C6 haloalkoxy or cyano.

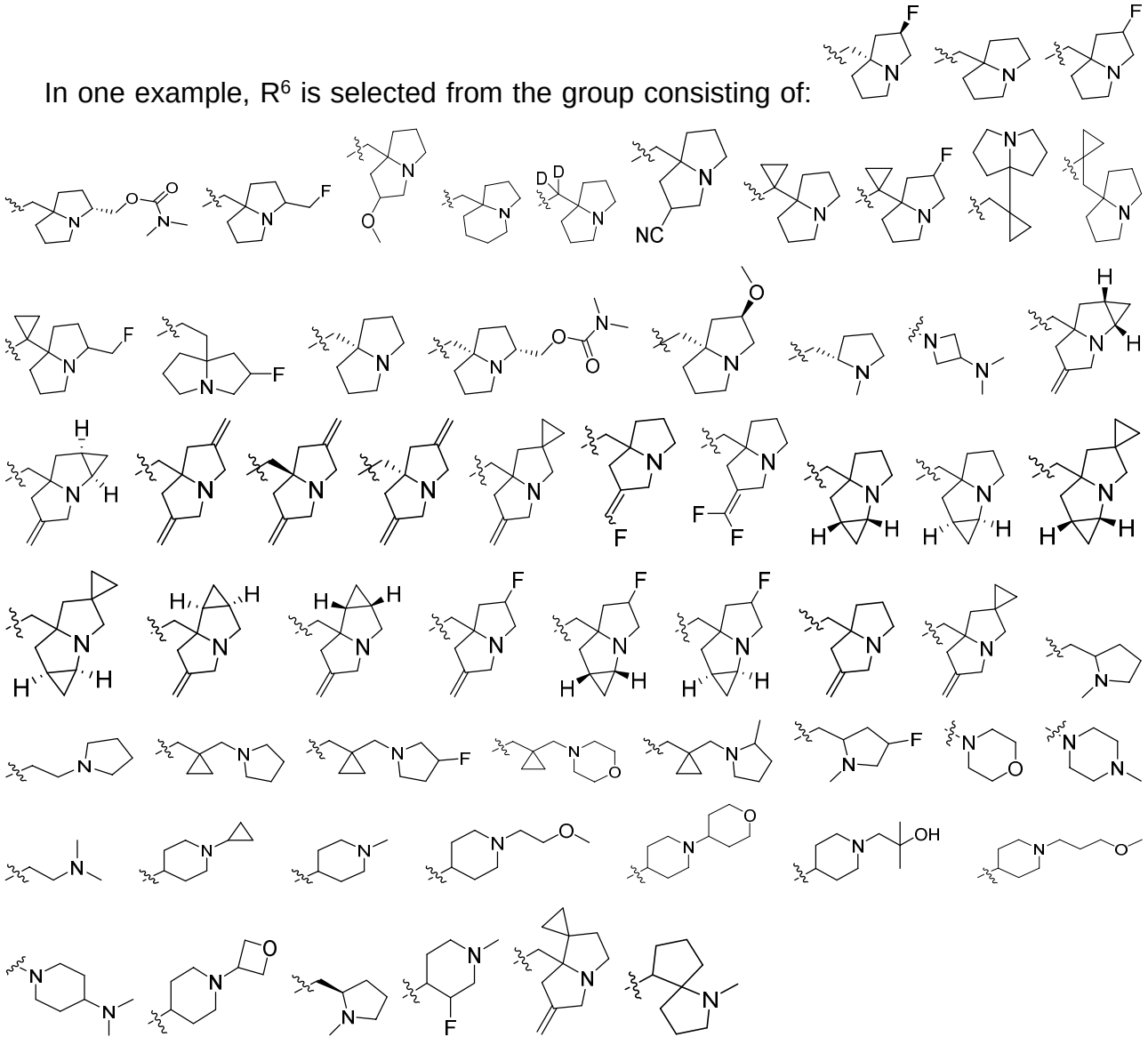
In one example, L_3 is O; R^6 is -L-hexahydro-1H-pyrrolizinyl, where L is C1-C4 alkylene; and 2 hydrogen atoms on one carbon atom in any 2 carbon atoms in the hexahydro-1H-pyrrolizinyl are both replaced by $=CR^{2a}R^{2b}$, where one pair of R^{2a} and R^{2b} is each independently hydrogen, halogen, cyano, C1-C4 alkyl or C1-C4 haloalkyl; and the other pair of R^{2a} and R^{2b}, together with the carbon atom to which they are attached, form a C3-C6 monocyclic cycloalkyl or a 3- to 6-membered monocyclic heterocyclyl; the C3-C6 monocyclic cycloalkyl or the 3- to 6-membered monocyclic heterocyclyl is optionally substituted with 1, 2, or 3 groups selected from halogen, cyano, C1-C4 alkyl, C1-C4 alkoxy, C1-C4 haloalkyl, C1-C4 haloalkoxy, C6-C10 aryl, or a 5- or 6-membered monocyclic heteroaryl. Preferably, the hexahydro-1H-pyrrolizinyl is further optionally substituted with 1 or more (for example, 1, 2, 3, 4 or 5) R^{6a}, where R^{6a} is each independently halogen, hydroxyl, C1-C6 hydroxylalkyl, C1-C6 alkyl, C2-C6 alkenyl, C2-C6 alkynyl, C1-C6 haloalkyl, C1-C6 alkoxy, C1-C6 haloalkoxy or cyano.

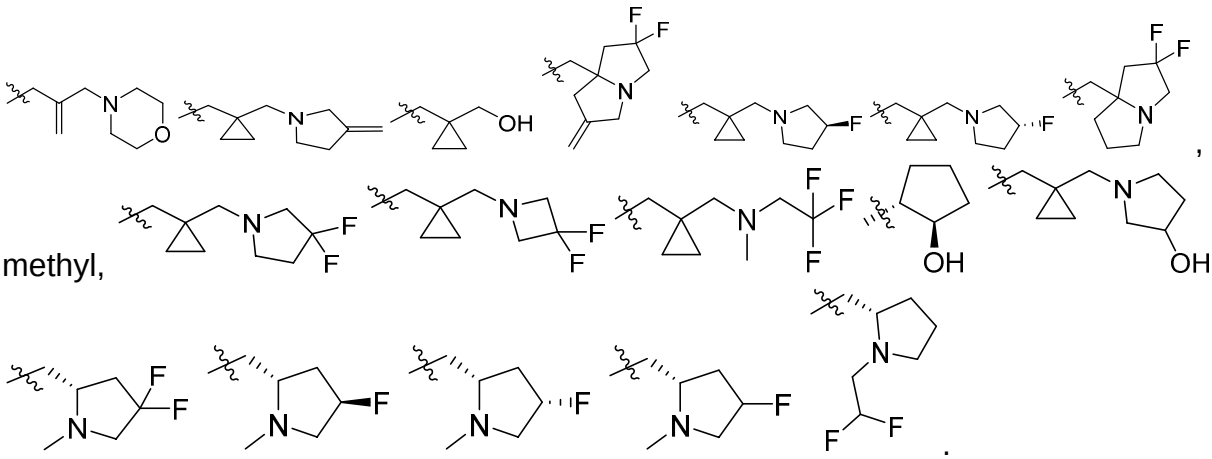
In one example, L_3 is O; R^6 is -L-hexahydro-1H-pyrrolizinyl, where L is C1-C4 alkylene; and 2 hydrogen atoms on one carbon atom in any 2 carbon atoms in the hexahydro-1H-pyrrolizinyl are both replaced by $=CR^{2a}R^{2b}$, where the two pairs of R^{2a} and R^{2b} are each independently, together with the carbon atom to which they are attached, form a C3-C6 monocyclic cycloalkyl or a 3- to 6-membered monocyclic heterocyclyl, in which the C3-C6 monocyclic cycloalkyl or the 3- to 6-membered monocyclic heterocyclyl is optionally

substituted with1, 2, or 3 groups selected from halogen, cyano, C1-C4 alkyl, C1-C4 alkoxy, C1-C4 haloalkyl, C1-C4 haloalkoxy, C6-C10 aryl, or a 5- or 6-membered monocyclic heteroaryl. Preferably, the hexahydro-1H-pyrrolizinyl is further optionally substituted with 1 or more (for example, 1, 2, 3, 4 or 5) R^{6a}, where R^{6a} is each independently halogen, hydroxyl, C1-C6 hydroxylalkyl, C1-C6 alkyl, C2-C6 alkenyl, C2-C6 alkynyl, C1-C6 haloalkyl, C1-C6 alkoxy, C1-C6 haloalkoxy or cyano.

In one example, L_3 is O; and R^6 is -L-hexahydro-1H-pyrrolizinyl, where L is C1-C4 alkylene; and the hexahydro-1H-pyrrolizinyl is substituted with 1 or more (for example, 1, 2, 3, 4 or 5) R^{6a}, where R^{6a} is each independently halogen, hydroxyl, C1-C6 hydroxylalkyl, C1-C6 alkyl, C2-C6 alkenyl, C2-C6 alkynyl, C1-C6 haloalkyl, C1-C6 alkoxy, C1-C6 haloalkoxy or cyano.

In one example, R^6 is selected from the group consisting of:





methyl,

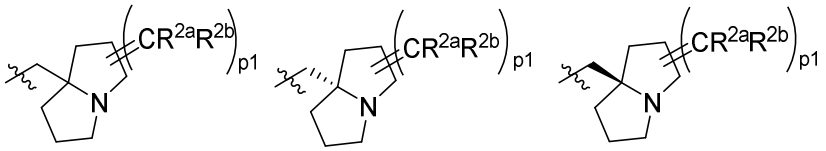
.

In one example, R^6 is a -L-6- to 10-membered fused heterocyclyl, where the 6- to 10-membered fused heterocyclyl has 1, 2, 3 or 4 heteratoms selected from N(R^m), S, S(=O), $S(=O)_2$, and O as the ring atom; and R^m is absent, hydrogen, C1-C4 alkyl, deuteratedC1-C4 alkyl, C1-C4 haloalkyl, C3-C20 cycloalkyl or 3- to 20-membered heterocyclyl, where L is a bond, C1-C4 alkylene or heteroaryl; the 6- to 10-membered fused heterocyclyl is saturated; 2 hydrogen atoms on the same carbon atom in any 1 or 2 carbon atoms in the 6- to 10-membered fused heterocyclyl are optionally both replaced by $=CR^{2a}R^{2b}$; the 6- to 10-membered fused heterocyclyl is optionally further substituted with 1 or more R^{6a}; and R^{2a}, R^{2b}, and R^{6a} are each as defined above. Preferably, R^{2a} and R^{2b} are each independently hydrogen, halo or C1-C4 alkyl, C1-C4 haloalkyl; and R^{6a} is halogen, hydroxyl, or C1-C6 alkyl.

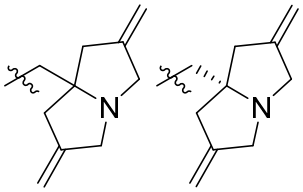
In one example, R^6 is a -L-6- to 10-membered fused heterocyclyl; and the 6- to 10-membered fused heterocyclyl is hexahydro-1H-pyrrolizinyl, where L is C1-C4 alkylene; 2 hydrogen atoms on the same carbon atom in any 1 or 2 carbon atoms in the 6- to 10-membered fused heterocyclyl are optionally both replaced by $=CR^{2a}R^{2b}$; the 6- to 10-membered fused heterocyclyl is optionally further substituted with 1 or more R^{6a}; and R^{2a}, R^{2b}, and R^{6a} are each as defined above. Preferably, R^{2a} and R^{2b} are each independently hydrogen, halo or C1-C4 alkyl, C1-C4 haloalkyl; and R^{6a} is halogen, hydroxyl, or C1-C6 alkyl.

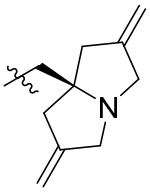
In one example, R^6 is a -L-6- to 10-membered fused heterocyclyl; and the 6- to 10-membered fused heterocyclyl is hexahydro-1H-pyrrolizinyl, where L is C1-C2 alkylene; 2 hydrogen atoms on the same carbon atom in any 1 or 2 carbon atoms in the 6- to 10-membered fused heterocyclyl are optionally both replaced by $=CR^{2a}R^{2b}$; the 6- to 10-membered fused heterocyclyl is optionally further substituted with 1 or more R^{6a}; R^{2a} and R^{2b} are each independently hydrogen or fluoro; and R^{6a} is halogen, hydroxyl or C1-C6 alkyl.

In one example, R^6 is selected from the group consisting of:



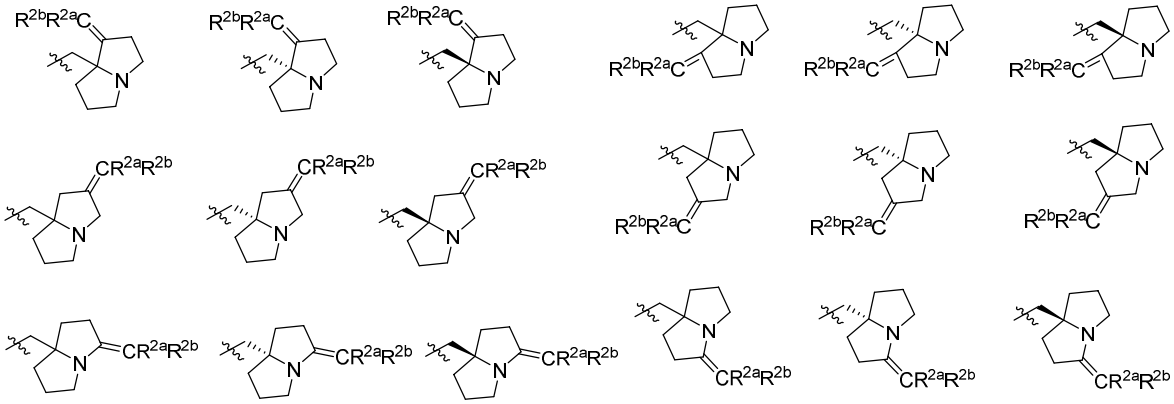
where in each formula, p1 is each independently 1 or 2; and R^{2a} and R^{2b} are each as defined above. Preferably, R^{2a} and R^{2b} are each independently hydrogen, halo or C1-C4 alkyl, C1-C4 haloalkyl. Preferably, the 1H-pyrrolizine is further optionally substituted with 1 or more R^{6a}; and R^{6a} is as defined above. Preferably, R^{6a} is each independently halo or C1-C6 alkoxy.

In one example, R^6 is selected from the group consisting of: 



.

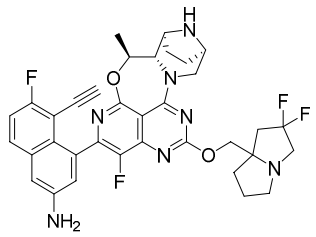
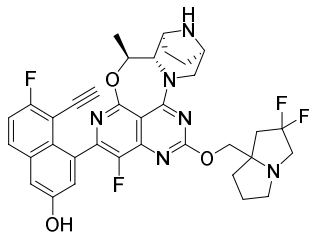
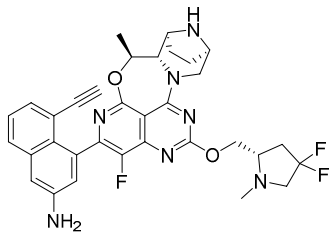
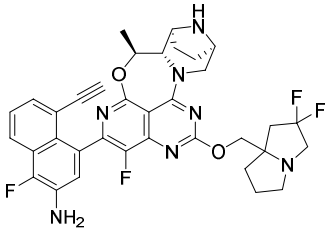
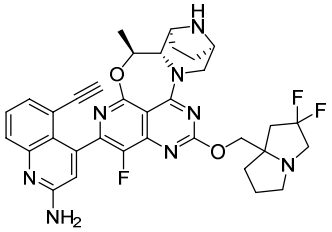
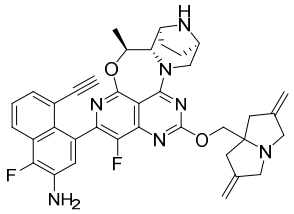
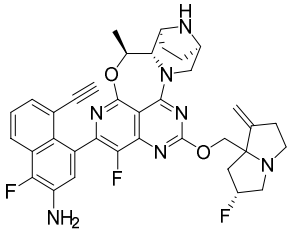
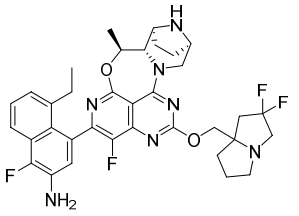
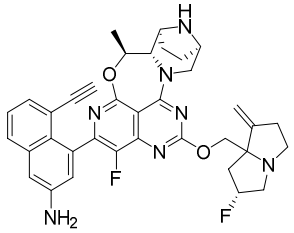
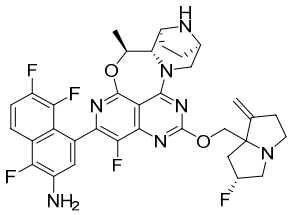
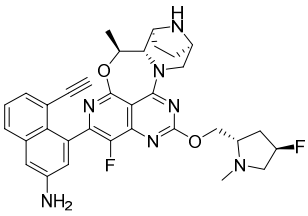
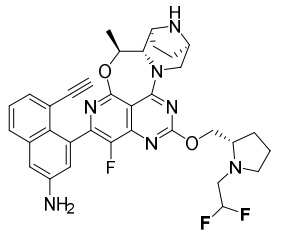
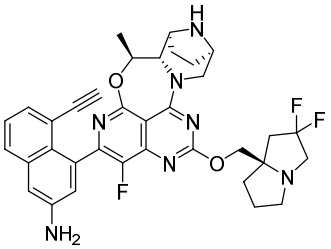
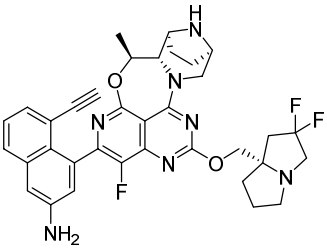
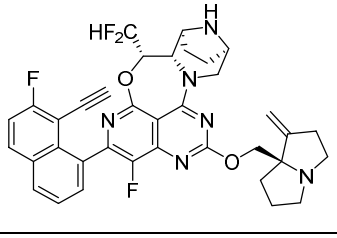
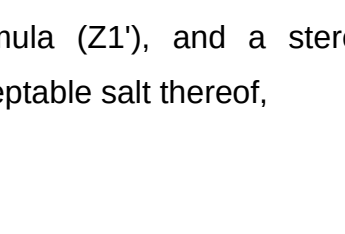
In one example, R^6 is selected from the group consisting of:



where in each formula, R^{2a} and R^{2b} are each as defined above. Preferably, R^{2a} and R^{2b} are each independently hydrogen, halo or C1-C4 alkyl, C1-C4 haloalkyl. Preferably, the 1H-pyrrolizine is further optionally substituted with 1 or more (for example, 2 or 3) R^{6a}; and R^{6a} is as defined above. Preferably, R^{6a} is each independently halo or C1-C6 alkoxy.

In some other examples, the compound is selected from Table (I):

Table (I)

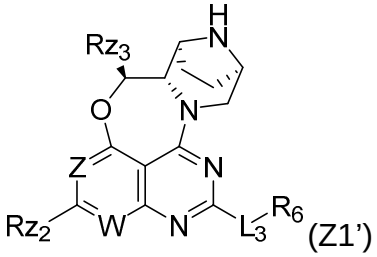
The first example of the present disclosure also provides a compound represented by Formula (Z1'), and a stereoisomer, a deuterated compound or a pharmaceutically acceptable salt thereof,

the 6- to 10-membered fused heterocyclyl is optionally substituted with 1 or 2 groups selected from deuterium, C1-C4 alkyl, C1-C4 haloalkyl, and halo; or 2 hydrogen atoms on the same carbon atom in any 1 or 2 carbon atoms in the 6- to 10-membered fused heterocyclyl are optionally both replaced by deuterium or $=CR^{2a}R^{2b}$, where R^{2a} and R^{2b} are each independently hydrogen, halogen, C1-C4 alkyl or C1-C4 haloalkyl; or each pair of R^{2a} and R^{2b} independently form, together with the carbon atom to which they are attached, a C3-C6 monocyclic cycloalkyl or a 3- to 6-membered monocyclic heterocyclyl; and

the 3- to 6-membered heterocyclyl or the 6- to 10-membered fused heterocyclyl is further optionally substituted with 1 or 2 groups selected from C1-C4 alkyl, C1-C4 haloalkyl, and halo;

the R^{62} is hydroxyl or halo; and R^{63} is C1-C4 alkyl, C1-C4 haloalkyl or halo.

In one aspect, the present disclosure refers to a compound represented by Formula (Z1'), or a stereoisomer, a deuterated compound or a pharmaceutically acceptable salt thereof,



(Z1')

wherein

W is N or CRz1, where Rz1 is hydrogen, halogen, C1-C6 alkyl or C1-C6 alkoxy;

Z is N or CRz11, where Rz11 is hydrogen, halogen, C1-C6 alkyl or C1-C6 alkoxy;

Rz2 is substituted or unsubstituted phenyl, naphthyl, quinoline, isoquinoline, benzo[b]thiophene, benzo[d]thiazole, indole, indazole or pyridine, where the substitution means that 1, 2, 3, 4 or 5 hydrogen atoms on phenyl, naphthyl, quinoline, isoquinoline, benzo[b]thiophene, benzo[d]thiazole, indole, indazole or pyridine are each independently replaced by R^1;

Rz3 is hydrogen, deuterium, methyl, deuterated methyl or halomethyl or $-CD_2F$ or $-CDF_2$;

R^1 is selected from the group consisting of: C1-C6 alkyl, halogen, hydroxyl, cyano, C1-C6 alkoxy, C1-C6 haloalkyl, C1-C6 haloalkoxy, cyano, $NR^{21}R^{22}$, $C(O)NR^{23}R^{24}$, CH_2R^{25}, $N=S(O)(C1\text{-}C6\ alkyl)_2$, $S(O)C1\text{-}C6\ alkyl$, $S(O)_2R^{26}$, -S-C1-C6 alkyl, C2-C6 alkenyl, C2-C6 alkynyl, C2-C6hydroxyalkynyl, C1-C6 cyanoalkyl, triazolyl, -S-C1-C6 haloalkyl, C1-C6 hydroxylalkyl, $-CH_2C(O)NR^{27}R^{28}$, -C2-C6 alkynyl-$NR^{29}R^{30}$, C2-C6 deuterated alkynyl, (C1-C6 alkoxy)C1-C6 haloalkyl- or cycloalkyl, where the cycloalkyl is optionally substituted with halo or C1-C6 alkyl, where

R^{21} is H, C1-C6 alkyl, C1-C6 haloalkyl, C(O)C1-C6 alkyl or C(O)OC1-C6 alkyl; R^{22} is H, C1-C6 alkyl or C1-C6 haloalkyl; or R^{21} and R^{22}, together with the nitrogen atom to which they are attached, form a 3- to 6-membered nitrogen-containing heterocyclic group, where the 3- to 6-membered nitrogen-containing heterocyclic group is optionally substituted with 1 or 2 groups selected from halogen, methyl, trifluoromethyl, methoxy and trifluoromethoxy;

R^{23} and R^{24} are each independently H, C1-C6 alkyl, or C1-C6 haloalkyl; or R^{23} and R^{24}, together with the nitrogen atom to which they are attached, form a 3- to 6-membered nitrogen-containing heterocyclic group, where the 3- to 6-membered nitrogen-containing heterocyclic group is optionally substituted with 1 or 2 groups selected from halogen, methyl, trifluoromethyl, methoxy, and trifluoromethoxy; and

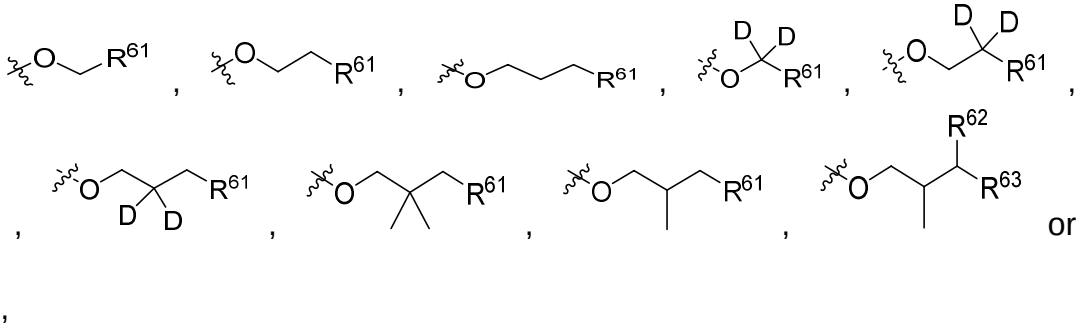
R^{25} is hydroxy, cyano, heterocyclyl, $NR^{251}R^{252}$, $C(O)NR^{253}R^{254}$ or $SO_2C1\text{-}C6\ alkyl$, where R^{251}, R^{252}, R^{253} and R^{254} are each independently H or C1-C6 alkyl; or R^{251} and R^{252}, together with the nitrogen atom to which they are attached, form a 3- to 6-membered nitrogen-containing heterocyclic group, where the 3- to 6-membered nitrogen-containing heterocyclic group is optionally substituted with 1 or 2 groups selected from halogen, methyl, trifluoromethyl, methoxy and trifluoromethoxy; or R^{253} and R^{254}, together with the nitrogen

atom to which they are attached, form a 3- to 6-membered nitrogen-containing heterocyclic group, where the 3- to 6-membered nitrogen-containing heterocyclic group is optionally substituted with 1 or 2 groups selected from halogen, methyl, trifluoromethyl, methoxy and trifluoromethoxy;

R^{26} is C1-C6 alkyl, C1-C6 haloalkyl, or $NR^{261}R^{262}$, where R^{261} and R^{262} are each independently H or C1-C6 alkyl, or R^{261} and R^{262}, together with the nitrogen atom to which they are attached, form a 3- to 6-membered nitrogen-containing heterocyclic group, where the 3- to 6-membered nitrogen-containing heterocyclic group is optionally substituted with 1 or 2 groups selected from halogen, methyl, trifluoromethyl, methoxy, and trifluoromethoxy;

R^{27} and R^{28} are each independently H, C1-C6 alkyl, or C1-C6 haloalkyl; or R^{27} and R^{28}, together with the nitrogen atom to which they are attached, form a 3- to 6-membered nitrogen-containing heterocyclic group, where the 3- to 6-membered nitrogen-containing heterocyclic group is optionally substituted with 1 or 2 groups selected from halogen, methyl, trifluoromethyl, methoxy, and trifluoromethoxy; and

R^{29} and R^{30} are each independently H, C1-C6 alkyl, or C1-C6 haloalkyl; or R^{29} and R^{30}, together with the nitrogen atom to which they are attached, form a 3- to 6-membered nitrogen-containing heterocyclic group, where the 3- to 6-membered nitrogen-containing heterocyclic group is optionally substituted with 1 or 2 groups selected from halogen, methyl, trifluoromethyl, methoxy, and trifluoromethoxy; and

$-L_3-R^6$ is , or

in which R^{61} is a 3- to 6-membered heterocyclyl or a 6- to 10-membered fused heterocyclyl, where

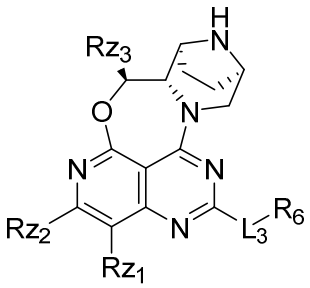
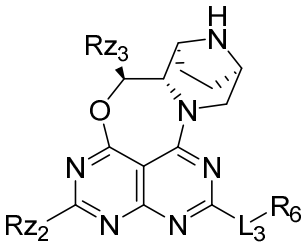
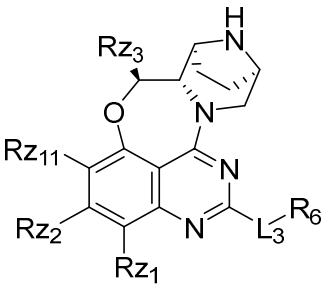
the 3- to 6-membered heterocyclyl is optionally substituted with 1 or 2 groups selected from deuterium, C1-C4 alkyl, C1-C4 haloalkyl, and halo; or 2 hydrogen atoms on the same carbon atom in any 1 or 2 carbon atoms in the 3- to 6-membered heterocyclyl are optionally both replaced by $=CR^{2a}R^{2b}$, where R^{2a} and R^{2b} are each independently hydrogen, halogen, C1-C4 alkyl or C1-C4 haloalkyl;

the 6- to 10-membered fused heterocyclyl is optionally substituted with 1 or 2 groups selected from deuterium, C1-C4 alkyl, C1-C4 haloalkyl, and halo; or 2 hydrogen atoms on the same carbon atom in any 1 or 2 carbon atoms in the 6- to 10-membered fused heterocyclyl are optionally both replaced by $=CR^{2a}R^{2b}$, where R^{2a} and R^{2b} are each independently hydrogen, halogen, C1-C4 alkyl or C1-C4 haloalkyl; or each pair of R^{2a} and R^{2b} independently form, together with the carbon atom to which they are attached, a C3-C6 monocyclic cycloalkyl or a 3- to 6-membered monocyclic heterocyclyl; and

the 3- to 6-membered heterocyclyl or the 6- to 10-membered fused heterocyclyl is further optionally substituted with 1 or 2 groups selected from C1-C4 alkyl, C1-C4 haloalkyl, and halo; and

R^{62} is hydroxyl or halo; and R^{63} is C1-C4 alkyl, C1-C4 haloalkyl or halo.

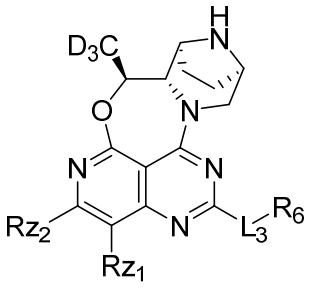
In one example, the compound represented by Formula (Z1') is a compound represented by Formula (Z1), Formula (Z2) or Formula (Z3):

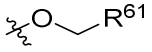
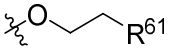
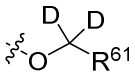
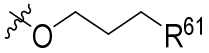
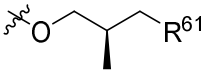

(Z1)

(Z2)

(Z3)

where in the formula, Rz11, Rz1, Rz2, Rz3, L_3, and R_6 are each as defined above.

In one example, Rz3 is methyl, deuterated methyl or halomethyl.

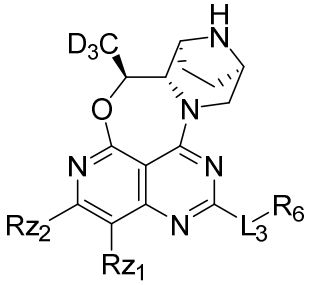
In one example, the compound represented by Formula (Z1') is a compound represented by Formula (Z), where in the formula, Rz1 and Rz2 are each as defined above;


(Z);

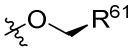
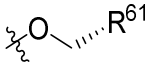
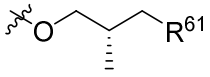
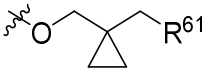
$-L_3-R^6$ is , , , , ,  or ; R^{61} is a 3- to 6-membered heterocyclyl or a 6- to 10-membered fused heterocyclyl; the 3- to 6-membered heterocyclyl is optionally substituted with 1 or 2 groups selected from C1-C4 alkyl, C1-C4 haloalkyl, and halo; and 2 hydrogen atoms on the same carbon atom in any 1 or 2 carbon atoms in the 6- to 10-membered fused

heterocyclyl are optionally both replaced by deuterium or $=CR^{2a}R^{2b}$, where R^{2a} and R^{2b} are each independently hydrogen, halogen, C1-C4 alkyl or C1-C4 haloalkyl.

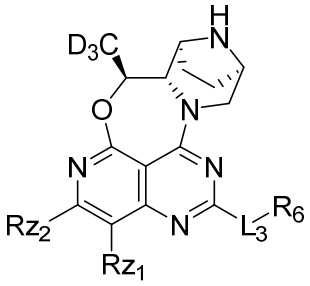
In one example, the compound represented by Formula (Z1') is a compound represented by Formula (Z):



(Z);

where in the formula, Rz1, Rz2, and R_6 are each as defined above; $-L_3-R^6$ is , ,  or ; and R^{61} is as defined above. When used as a KRAS G12D inhibitor, the compound represented by Formula (Z) of the present disclosure has better bioavailability and higher AUC.

In one example, the compound represented by Formula (Z1') is a compound represented by Formula (Z):



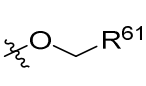
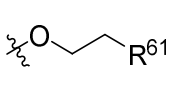
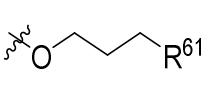
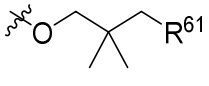
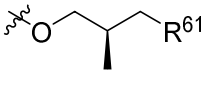
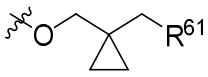
(Z);

where in the formula,

Rz1 is halo or hydrogen;

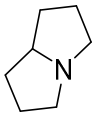
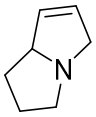
Rz2 is a substituted or unsubstituted phenyl, naphthyl or pyridine, where the substitution means that 1, 2, 3, 4 or 5 hydrogen atoms on the phenyl, naphthyl or pyridine are independently replaced by R^1;

R^1 is selected from the group consisting of: C1-C6 alkyl, halogen, hydroxyl, cyano, C1-C6 alkoxy, C1-C6 haloalkyl, C1-C6 haloalkoxy, cyano, $NR^{21}R^{22}$, $C(O)NR^{23}R^{24}$, CH_2R^{25}, $N=S(O)(C1\text{-}C6\ alkyl)_2$, $S(O)C1\text{-}C6\ alkyl$, $S(O)_2R^{26}$, -S-C1-C6 alkyl, C2-C6 alkenyl, C2-C6 alkynyl, C2-C6hydroxyalkynyl, C1-C6 cyanoalkyl, triazolyl, -S-C1-C6 haloalkyl, C1-C6 hydroxylalkyl, $-CH_2C(O)NR^{27}R^{28}$, -C2-C6 alkynyl-$NR^{29}R^{30}$, C2-C6 deuterated alkynyl, (C1-C6 alkoxy)C1-C6 haloalkyl- or cycloalkyl, where the cycloalkyl is optionally substituted with halo or C1-C6 alkyl, where

-L_3-R^6 is , , , ,  or ; R^{61} is 3- to 6-membered heterocyclyl or 6- to 10-membered fused heterocyclyl; the 3- to 6-membered heterocyclyl is optionally substituted with 1 or 2 groups selected from C1-C4 alkyl, C1-C4 haloalkyl, and halo; 2 hydrogen atoms on the same carbon atom in any 1 or 2 carbon atoms in the 6- to 10-membered fused heterocyclyl are optionally both replaced by $=CR^{2a}R^{2b}$, where R^{2a} and R^{2b} are each independently hydrogen, halogen, C1-C4 alkyl or C1-C4 haloalkyl.

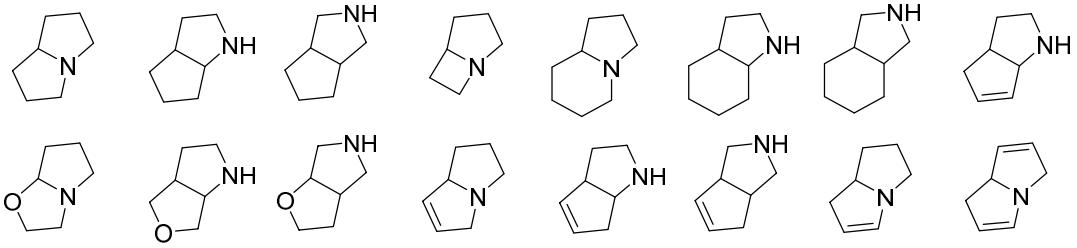
In one example, Rz11 is chloro or hydrogen.

In one example, Rz1 is fluoro or hydrogen.

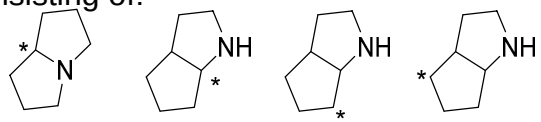
In one example, R^{61} is a 6- to 10-membered fused heterocyclyl; the 6- to 10-membered fused heterocyclyl is  or ; the 6- to 10-membered fused heterocyclyl is optionally substituted with 1 or 2 groups selected from deuterium, C1-C4 alkyl, C1-C4 haloalkyl, and halo; or 2 hydrogen atoms on the same carbon atom in any 1 or 2 carbon atoms in the 6- to 10-membered fused heterocyclyl are optionally both replaced by $=CR^{2a}R^{2b}$, where R^{2a} and R^{2b} are each independently hydrogen, halogen, C1-C4 alkyl or C1-C4 haloalkyl; and the 6- to 10-membered fused heterocyclyl is further optionally substituted with 1 or 2 groups selected from C1-C4 alkyl, C1-C4 haloalkyl, and halo.

In one example, R^{61} is a 3- to 6-membered heterocyclyl; the 3- to 6-membered heterocyclyl is tetrahydropyrrolyl, piperidinyl, piperazinyl or morpholinyl; the 3- to 6-membered heterocyclyl is optionally substituted with 1 or 2 groups selected from C1-C4 alkyl, C1-C4 haloalkyl, and halo; or 2 hydrogen atoms on the same carbon atom in any 1 or 2 carbon atoms in the 3- to 6-membered heterocyclyl are optionally both replaced by $=CR^{2a}R^{2b}$, where R^{2a} and R^{2b} are each independently hydrogen, halogen, C1-C4 alkyl or C1-C4 haloalkyl; and the 3- to 6-membered heterocyclyl is further optionally substituted with 1 or 2 groups selected from C1-C4 alkyl, C1-C4 haloalkyl, and halo.

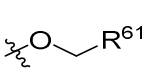
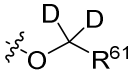
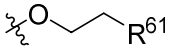
In one example, the 6 to 10 membered fused heterocyclyl is selected from the group consisting of:

.

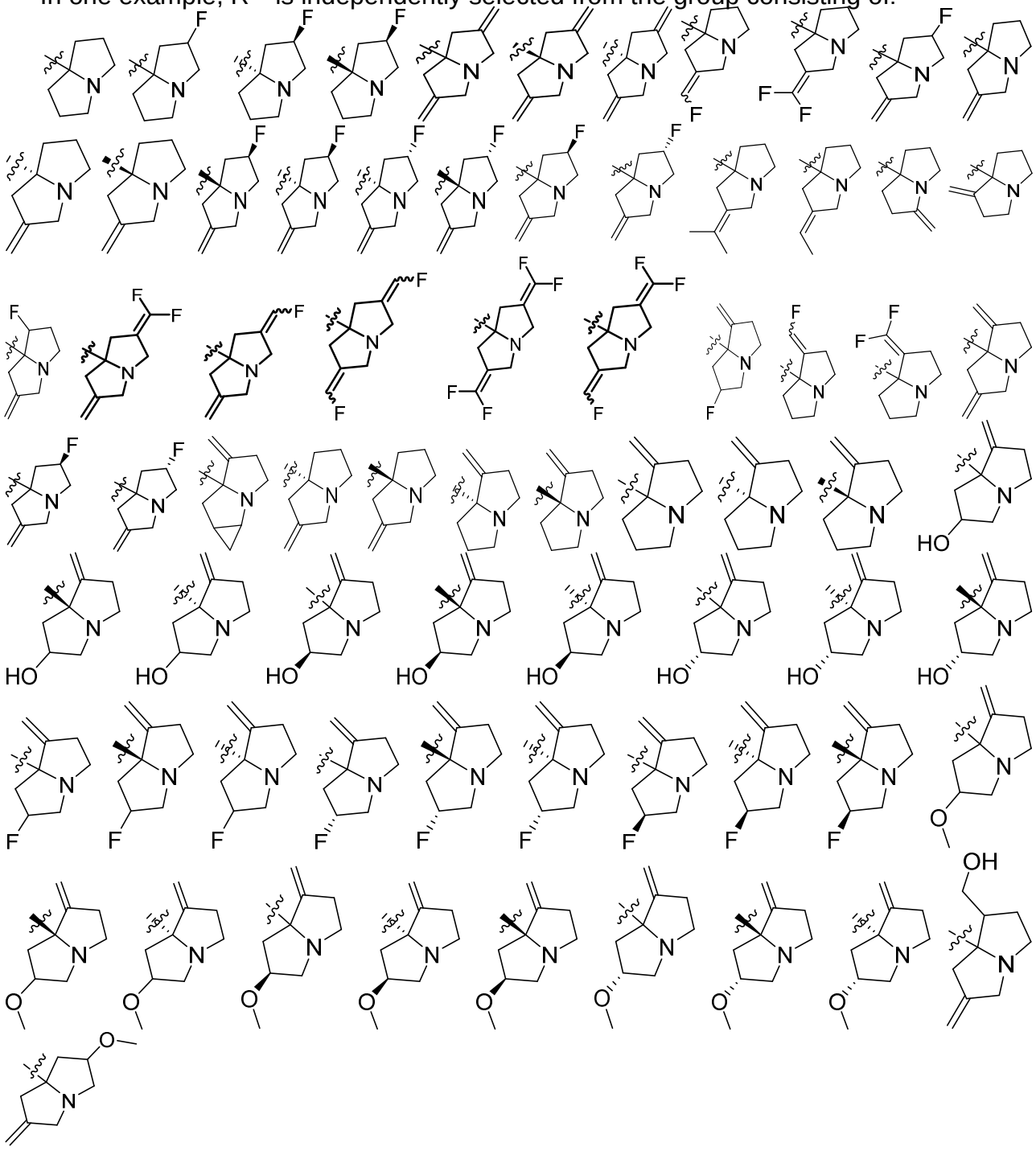
In one example, the 6 to 10 membered fused heterocyclyl is selected from the group consisting of:

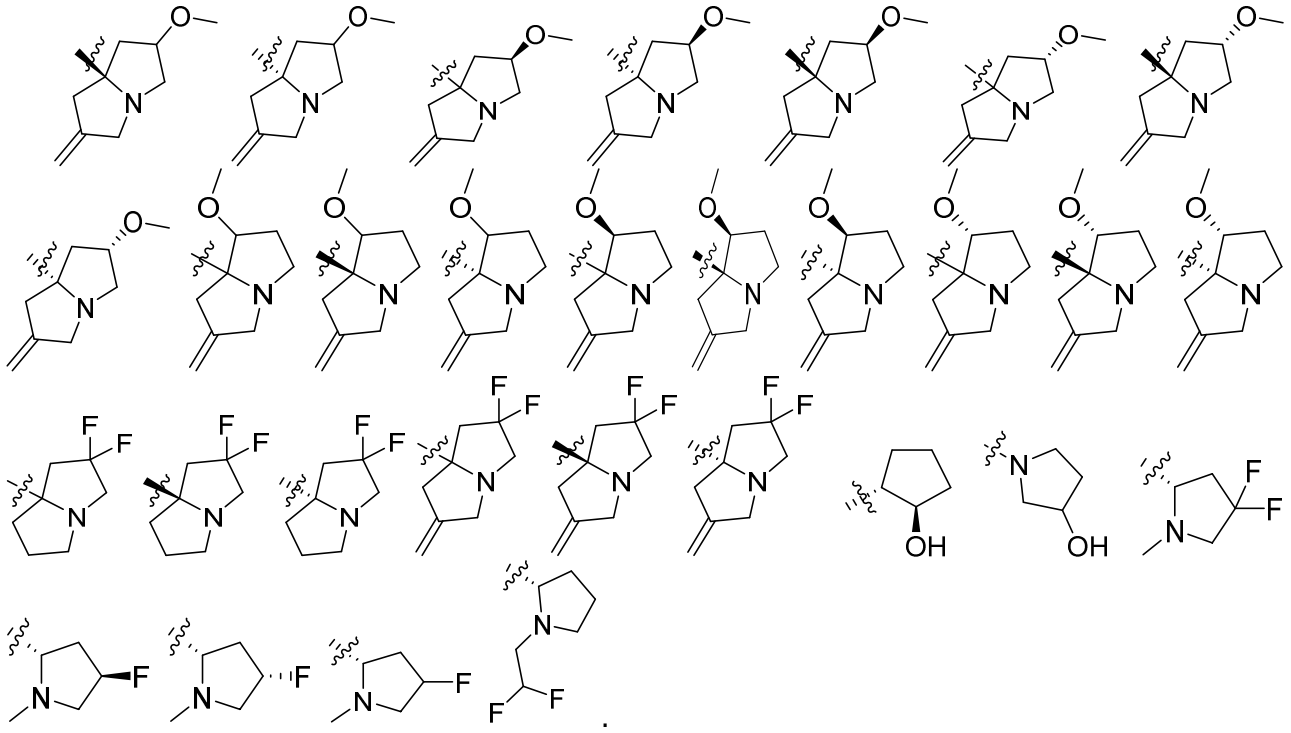


, where the carbon atom marked with * is a carbon atom attached to the rest of the molecule.

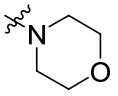
In one example, $-L_3-R^6$ is ,  or .

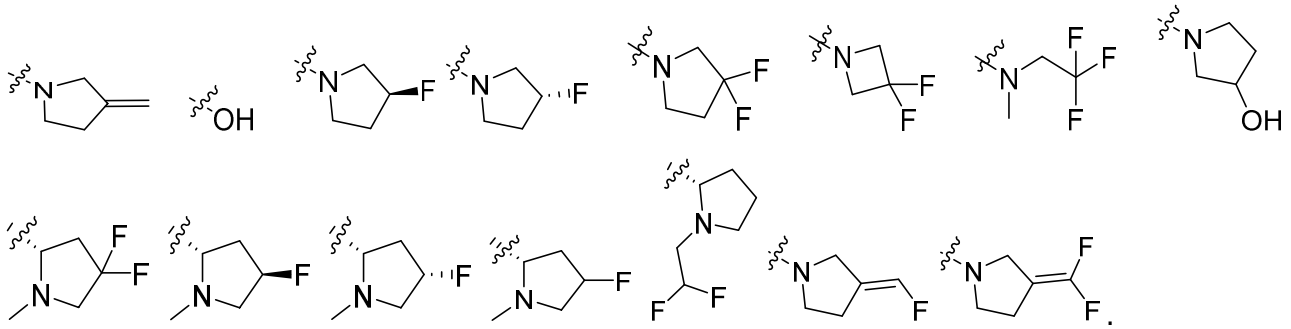
In one example, R^{61} is independently selected from the group consisting of:

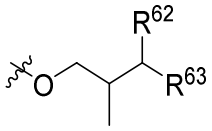




In one example, -L_3-R^6 is .

In one example, R^{61} is independently selected from the group consisting of: 

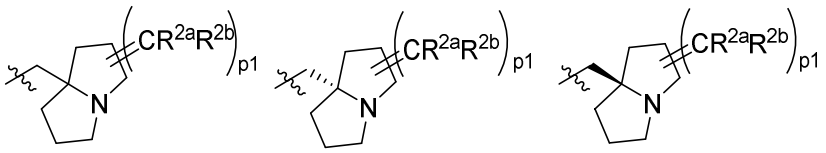


In one example, -L_3-R^6 is .

In one example, R^{62} is hydroxyl or halo; and R^{63} is methyl, ethyl, fluoromethyl, difluoromethyl or trifluoromethyl.

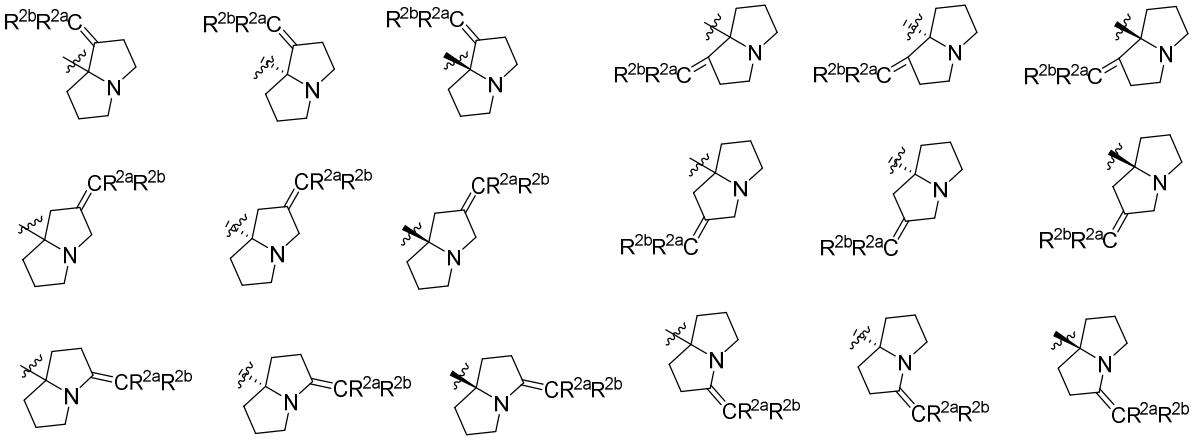
In one example, R^{62} is hydroxyl, and R^{63} is difluoromethyl.

In one example, R^6 is selected from the group consisting of:

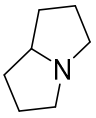


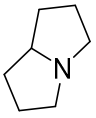
where in each formula, p1 is each independently 1 or 2; and R^{2a} and R^{2b} are each as defined above. Preferably, R^{2a} and R^{2b} are each independently hydrogen, halo or C1-C4 alkyl, C1-C4 haloalkyl. Preferably, the 1H-pyrrolizine is further optionally substituted with 1 or more R^{6a}; and R^{6a} is as defined above. Preferably, R^{6a} is each independently halo or C1-C6 alkoxy.

In one example, R^{61} is selected from the group consisting of:

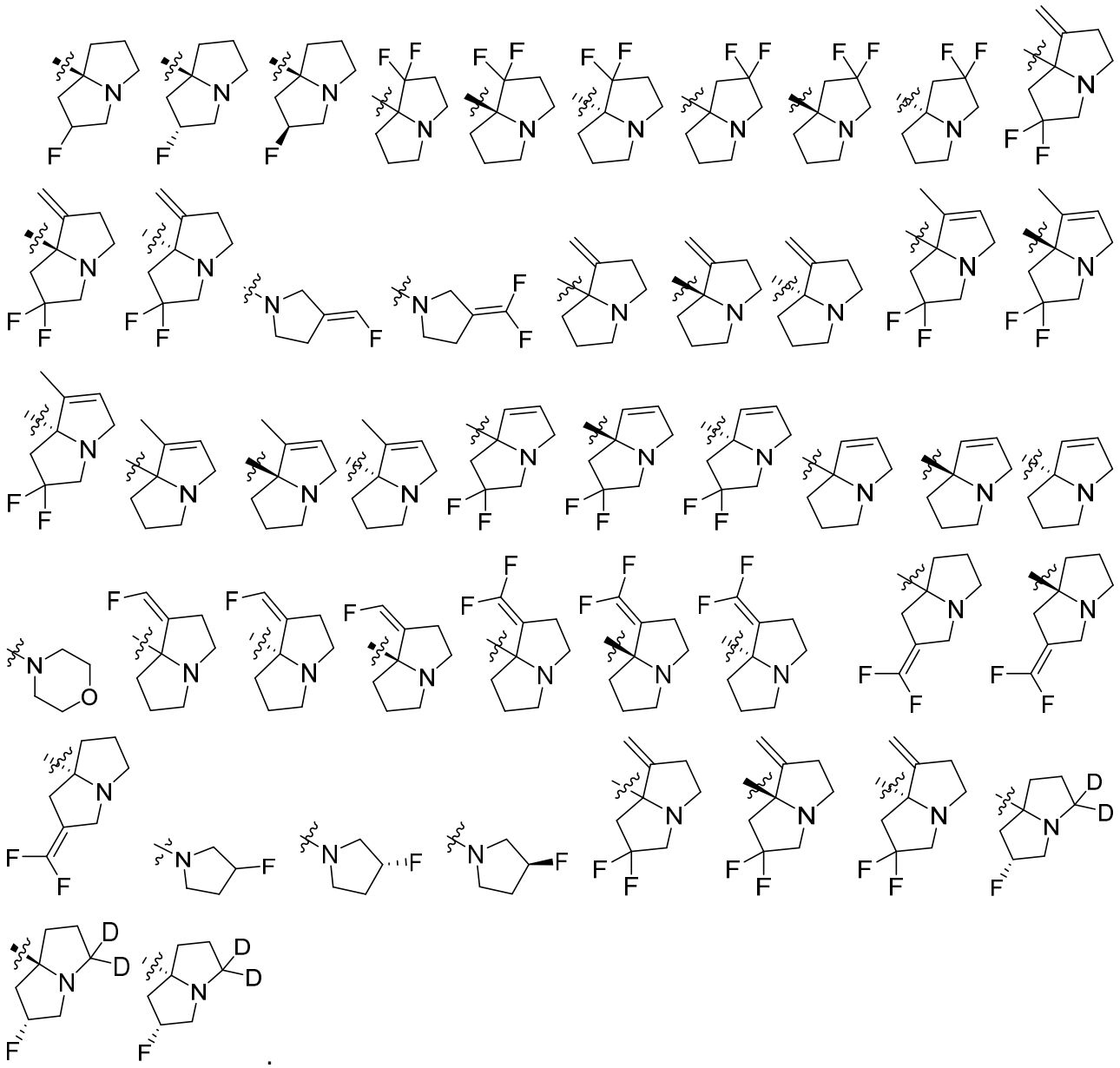


where in each formula, R^{2a} and R^{2b} are each independently hydrogen, halogen, C1-C4 alkyl or C1-C4 haloalkyl; or each pair of R^{2a}, R^{2b} independently form, together with the carbon atom to which they are attached, a C3-C6 monocyclic cycloalkyl or a 3- to 6-membered monocyclic heterocyclyl.

In one example, in the above substituents,  is optionally further substituted with 1 or 2 R^{6a}, in which R^{6a} is each independently hydrogen, deuterium or halo.

In one example, in the above substituents,  is optionally further substituted with 1 or 2 R^{6a}, in which R^{6a} is each independently deuterium or halo.

In one example, R^{61} is selected from the group consisting of:



In one example, R^1 is selected from: C1-C3 alkyl, halogen, hydroxyl, C1-C3 alkoxy, C1-C3 haloalkyl, C1-C3 haloalkoxy, cyano, $NR^{21}R^{22}$, $C(O)NR^{23}R^{24}$, CH_2R^{25}, $N=S(O)(C1\text{-}C3\ alkyl)_2$, $S(O)C1\text{-}C3\ alkyl$, $S(O)_2R^{26}$, -S-C1-C3 alkyl, C2-C4 alkenyl, C2-C4 alkynyl, C2-C4hydroxyalkynyl, C1-C3 cyanoalkyl, triazolyl, -S-C1-C3 haloalkyl, C1-C3 hydroxylalkyl, $-CH_2C(O)NR^{27}R^{28}$, -C2-C4 alkynyl$NR^{29}R^{30}$, C2-C4 deuterated alkynyl, (C1-C3 alkoxy)C1-C3 haloalkyl- or cycloalkyl, where the cycloalkyl is optionally substituted with halo or C1-C3 alkyl, where

R^{21} is H, C1-C3 alkyl, C1-C3 haloalkyl, C(O)C1-C3 alkyl or C(O)OC1-C3 alkyl; R^{22} is H, C1-C3 alkyl or C1-C3 haloalkyl; or R^{21} and R^{22}, together with the nitrogen atom to which they are attached, form a 3- to 6-membered nitrogen-containing heterocyclic group, where the 3- to 6-membered nitrogen-containing heterocyclic group is optionally substituted with 1 or 2 groups selected from halogen, methyl, trifluoromethyl, methoxy and trifluoromethoxy;

R^{23} and R^{24} are each independently H, C1-C3 alkyl, or C1-C3 haloalkyl; or R^{23} and R^{24}, together with the nitrogen atom to which they are attached, form a 3- to 6-membered nitrogen-containing heterocyclic group, where the 3- to 6-membered nitrogen-containing heterocyclic group is optionally substituted with 1 or 2 groups selected from halogen, methyl, trifluoromethyl, methoxy, and trifluoromethoxy;

R^{25} is hydroxyl, cyano, heterocyclyl, $NR^{251}R^{252}$, $C(O)NR^{253}R^{254}$ or SO_2C1-C3 alkyl, where R^{251}, R^{252}, R^{253}, and R^{254} are each independently H or C1-C3 alkyl; R^{251} and R^{252}, together with the nitrogen atom to which they are attached, form a 3- to 6-membered nitrogen containing heterocyclic group, where the 3- to 6-membered nitrogen containing heterocyclic group is optionally substituted with 1 or 2 groups selected from halogen, methyl, trifluoromethyl, methoxy, and trifluoromethoxy; and R^{253} and R^{254}, together with the nitrogen atom to which they are attached, form a 3- to 6-membered nitrogen containing heterocyclic group, where the 3- to 6-membered nitrogen containing heterocyclic group is optionally substituted with 1 or 2 groups selected from halogen, methyl, trifluoromethyl, methoxy, and trifluoromethoxy;

R^{26} is C1-C3 alkyl, C1-C3 haloalkyl, or $NR^{261}R^{262}$, where R^{261} and R^{262} are each independently H or C1-C3 alkyl, or R^{261} and R^{262}, together with the nitrogen atom to which they are attached, form a 3- to 6-membered nitrogen-containing heterocyclic group, where the 3- to 6-membered nitrogen-containing heterocyclic group is optionally substituted with 1 or 2 groups selected from halogen, methyl, trifluoromethyl, methoxy, and trifluoromethoxy;

R^{27} and R^{28} are each independently H, C1-C3 alkyl, or C1-C3 haloalkyl; or R^{27} and R^{28}, together with the nitrogen atom to which they are attached, form a 3- to 6-membered nitrogen-containing heterocyclic group, where the 3- to 6-membered nitrogen-containing heterocyclic group is optionally substituted with 1 or 2 groups selected from halogen, methyl, trifluoromethyl, methoxy, and trifluoromethoxy;

R^{29} and R^{30} are each independently H, C1-C3 alkyl, or C1-C3 haloalkyl; or R^{29} and R^{30}, together with the nitrogen atom to which they are attached, form a 3- to 6-membered nitrogen-containing heterocyclic group, where the 3- to 6-membered nitrogen-containing heterocyclic group is optionally substituted with 1 or 2 groups selected from halogen, methyl, trifluoromethyl, methoxy, and trifluoromethoxy.

In one example, Rz2 is substituted or unsubstituted phenyl, naphthalenyl or pyridinyl, where the substitution means that 1, 2 or 3 hydrogen atoms on the phenyl, naphthalenyl or pyridinyl are each independently substituted with R^1; and R^1 is selected from the group consisting of: C1-C6 alkyl, halogen, C1-C6 haloalkyl, $NR^{21}R^{22}$; R^{21} is H, C1-C3 alkyl, C1-C3 haloalkyl, C(O)C1-C3 alkyl or C(O)OC1-C3 alkyl; R^{22} is H, C1-C3 alkyl or C1-C3 haloalkyl;

or R^{21} and R^{22}, together with the nitrogen atom to which they are attached, form a 3- to 6-membered nitrogen containing heterocyclic group, where the 3- to 6-membered nitrogen containing heterocyclic group is optionally substituted with 1 or 2 groups selected from halogen, methyl, trifluoromethyl, methoxy, and trifluoromethoxy. Preferably, R^{21} is H; and R^{22} is H.

In one example, Rz2 is phenyl substituted with 1, 2, 3 or 4 R^1, where each R^1 is each independently halogen, hydroxyl, ethynyl, methyl, methyl-O-, methyl-S-, trifluoromethyl, trifluoromethyl-O-, amino, isopropyl, or cyclopropyl; and the cyclopropyl is optionally substituted with halo or methyl. Preferably, one R^1 is ethynyl, and the remaining R^1 is each independently halogen, hydroxyl, ethynyl, methyl, methyl-O-, methyl-S-, trifluoromethyl, trifluoromethyl-O-, amino, isopropyl or cyclopropyl; and the cyclopropyl is optionally substituted with halo or methyl.

In one example, Rz2 is phenyl substituted with 1, 2 or 3 R^1, where each R^1 is each independently halogen, hydroxyl, ethynyl, methyl, methyl-O-, methyl-S-, trifluoromethyl, trifluoromethyl-O-, amino, isopropyl or cyclopropyl.

In one example, Rz2 is naphthalenyl substituted with 1, 2, 3 or 4 R^1, where each R^1 is each independently halogen, hydroxyl, ethynyl, methyl, methyl-O-, methyl-S-, trifluoromethyl, trifluoromethyl-O-, amino, isopropyl, cyano or cyclopropyl; and the cyclopropyl is optionally substituted with halo or methyl. Preferably, one R^1 is ethynyl, and the remaining R^1 is each independently halogen, hydroxyl, ethynyl, methyl, methyl-O-, methyl-S-, trifluoromethyl, trifluoromethyl-O-, amino, isopropyl or cyclopropyl; and the cyclopropyl is optionally substituted with halo or methyl.

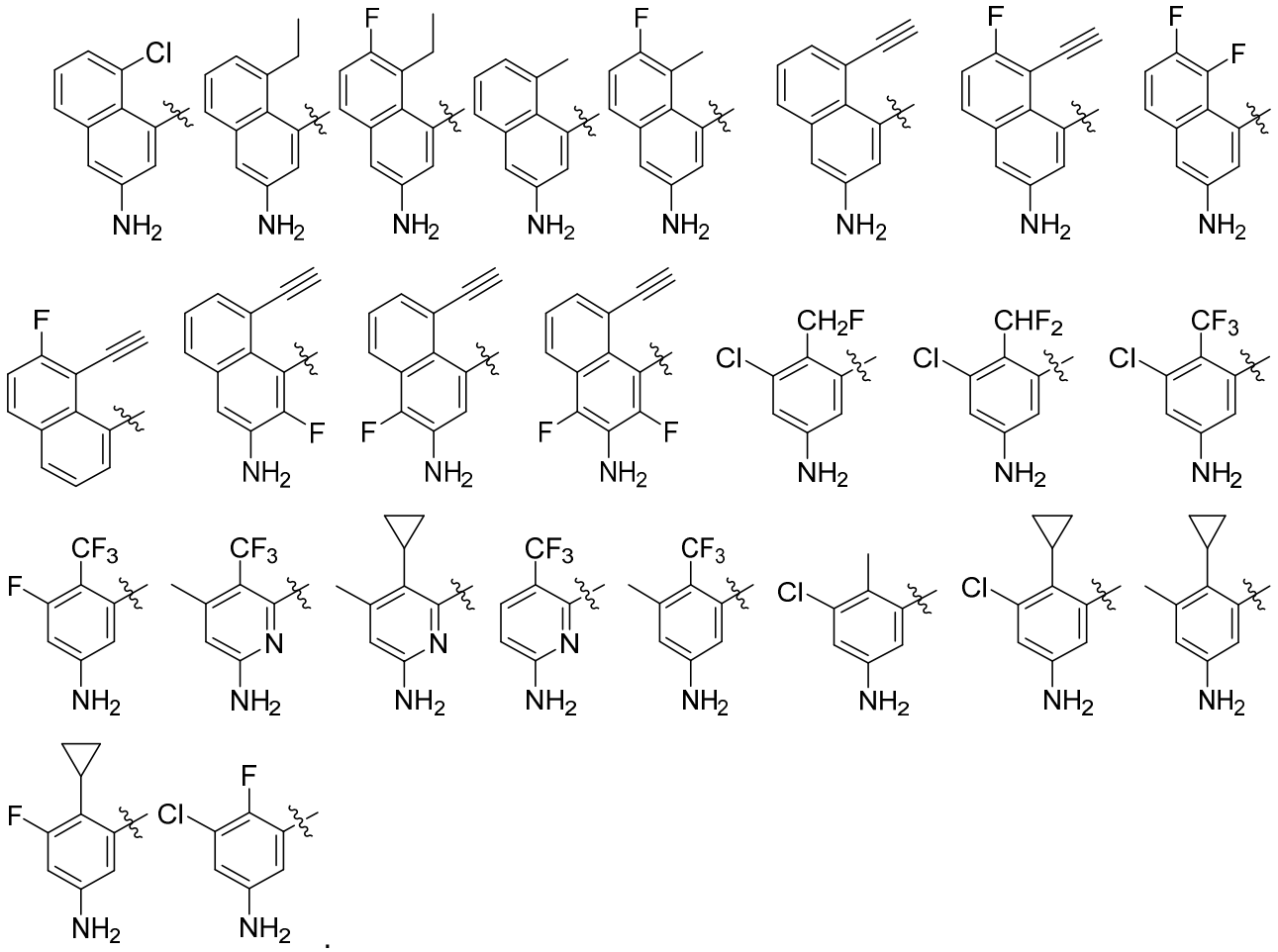
In one example, Rz2 is naphthalenyl substituted with 1, 2 or 3 R^1, where each R^1 is each independently halogen, hydroxyl, ethynyl, methyl, ethyl, amino, cyano or difluoromethyl. Preferably, one R^1 is ethynyl, and the remaining R^1 is each independently halogen, hydroxyl, ethynyl, methyl, methyl-O-, methyl-S-, trifluoromethyl, trifluoromethyl-O-, amino, isopropyl or cyclopropyl; and the cyclopropyl is optionally substituted with halo or methyl.

In one example, Rz2 is naphthalenyl substituted with 1 or 2 R^1, where each R^1 is each independently halogen, ethynyl, or amino.

In one example, Rz2 is pyridinyl substituted with 1, 2, 3 or 4 R^1, where each R^1 is each independently halogen, hydroxyl, ethynyl, methyl, methyl-O-, methyl-S-, trifluoromethyl, trifluoromethyl-O-, amino, isopropyl, or cyclopropyl; and the cyclopropyl is optionally substituted with halo or methyl. Preferably, one R^1 is ethynyl, and the remaining R^1 is each independently halogen, hydroxyl, ethynyl, methyl, methyl-O-, methyl-S-,

trifluoromethyl, trifluoromethyl-O-, amino, isopropyl or cyclopropyl; and the cyclopropyl is optionally substituted with halo or methyl.

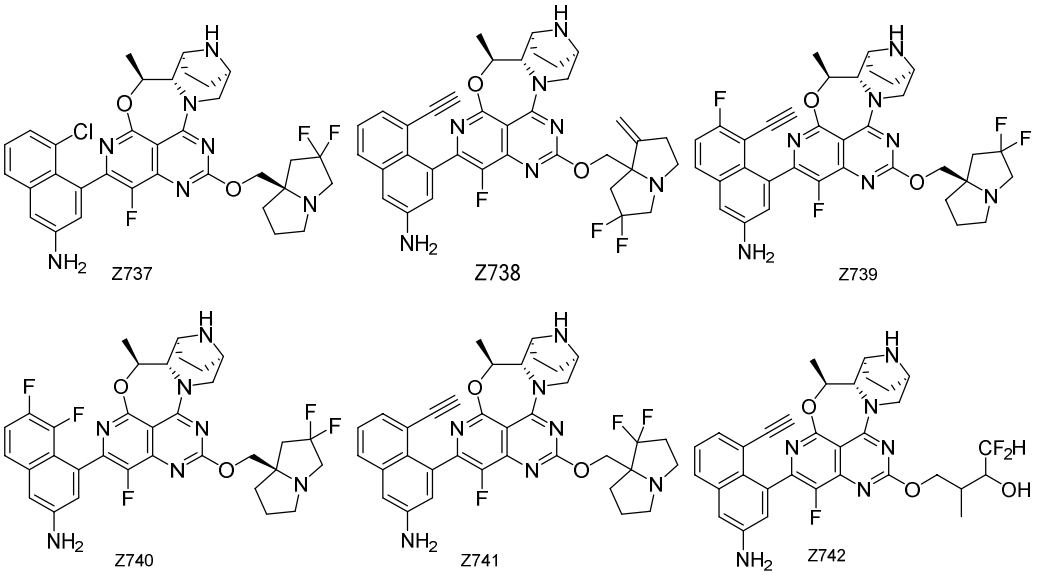
In one example, Rz2 is selected from the group consisting of:

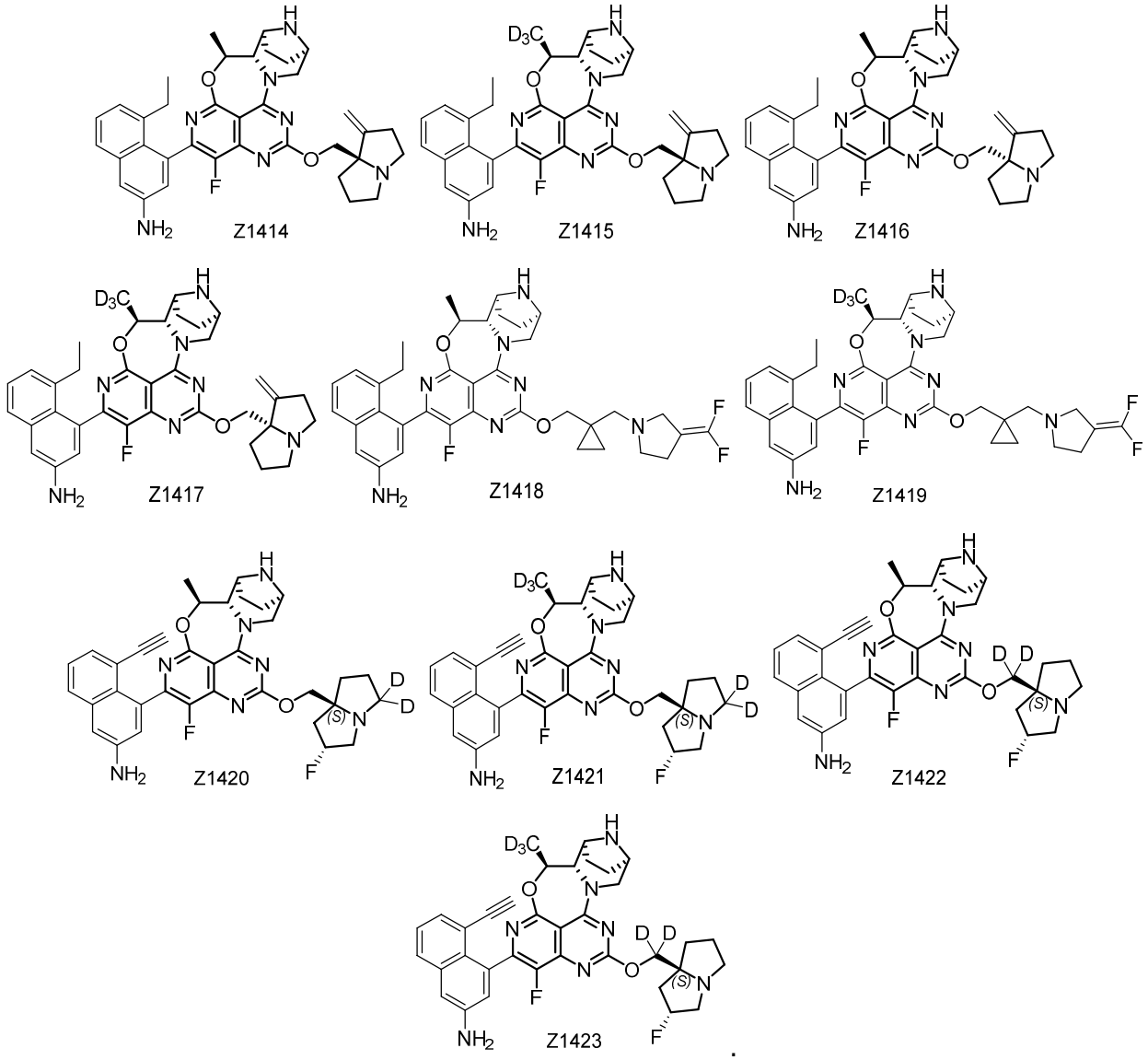


.

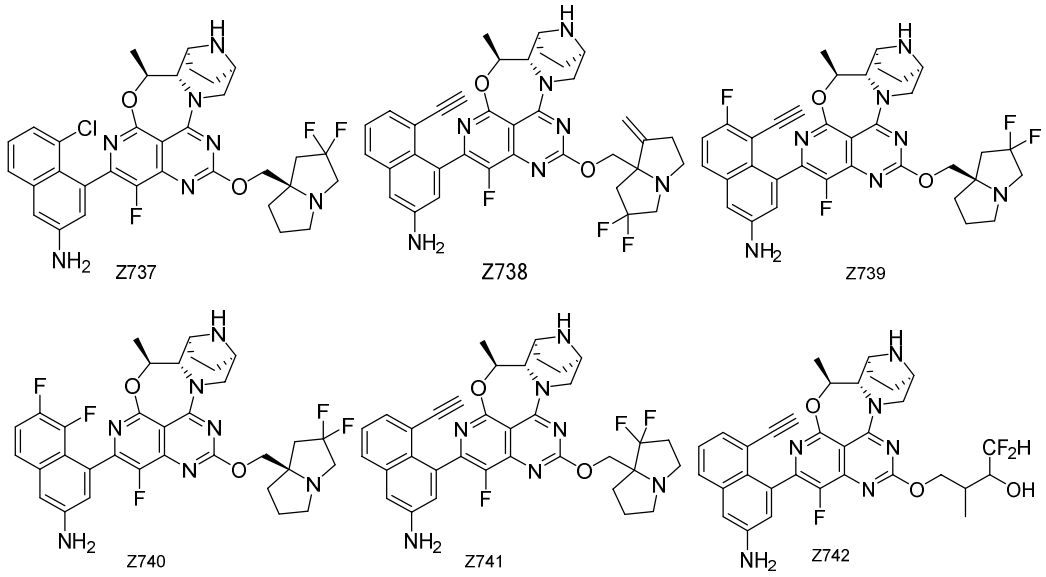
In some other examples, the compound is selected from Table A

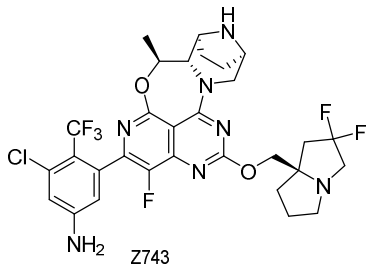
In some other examples, the compound is selected from the group consisting of:

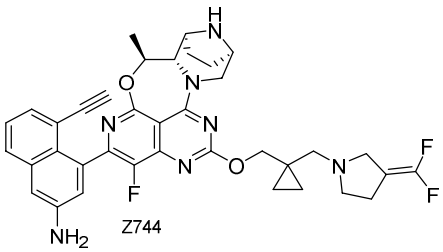


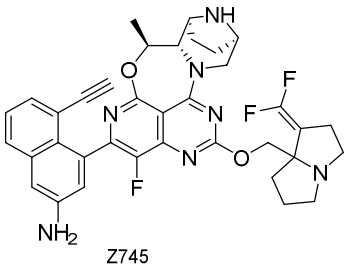


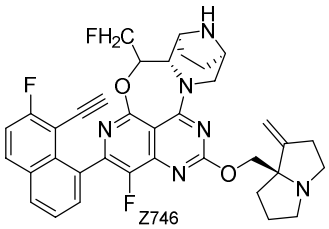
In one aspect, the present disclosure refers to a compound, or a stereoisomer, a deuterated compound or a pharmaceutically acceptable salt thereof, wherein the compound is selected from Table A or from the group consisting of:

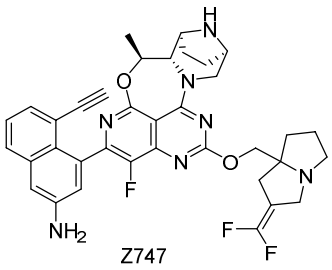


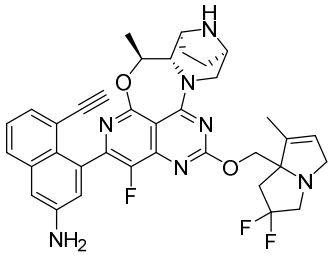

Z743

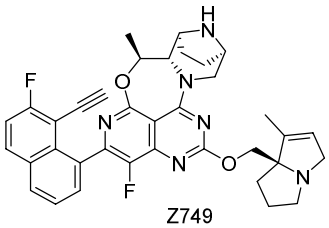

Z744

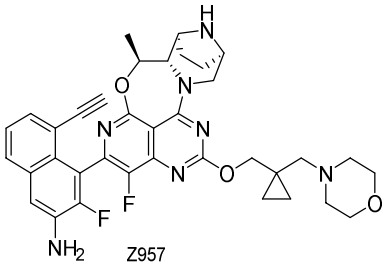

Z745

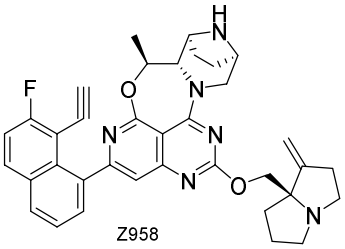

Z746

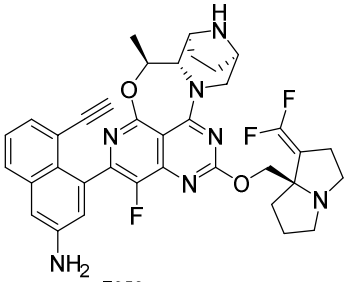

Z747

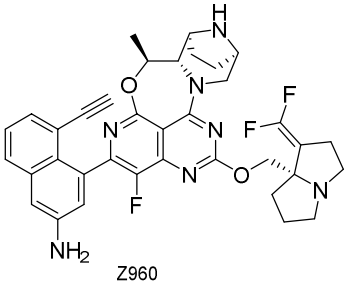

Z748

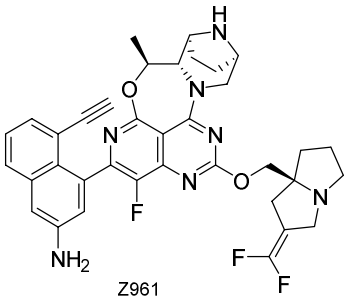

Z749

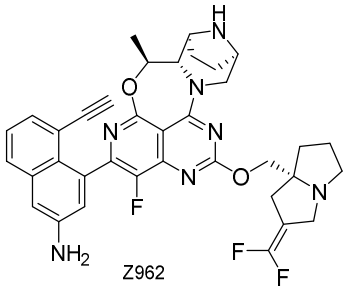

Z957

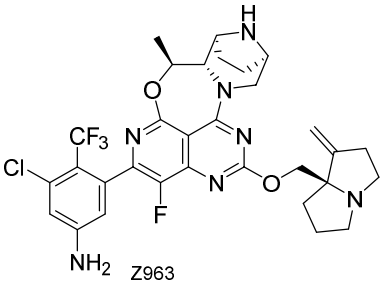

Z958

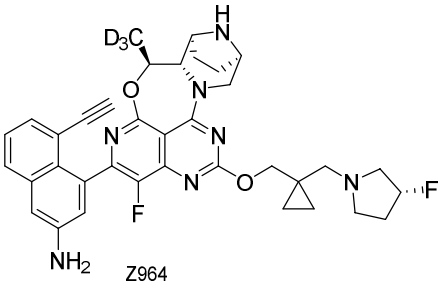

Z959

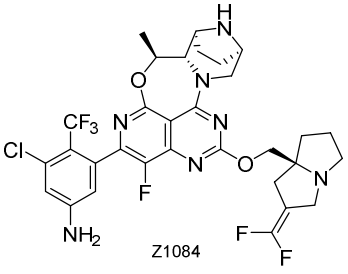

Z960

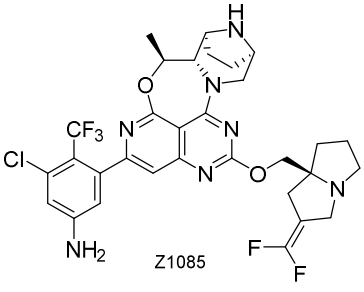

Z961

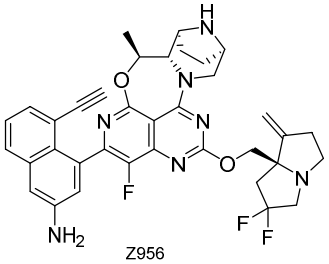

Z962

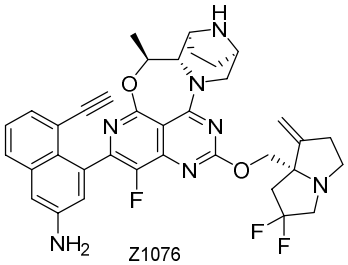

Z963

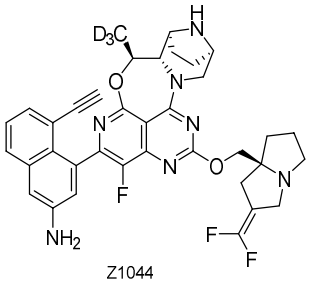

Z964

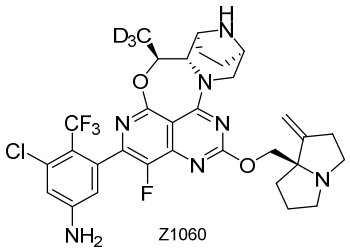

Z1084

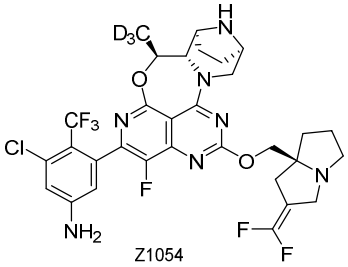

Z1085

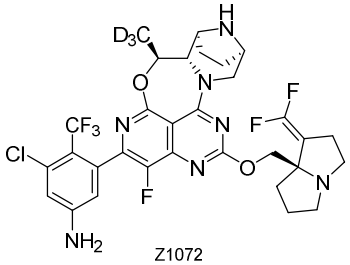

Z956

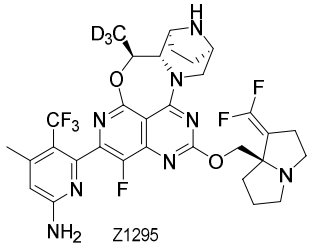

Z1076

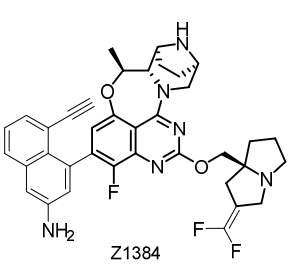

Z1044

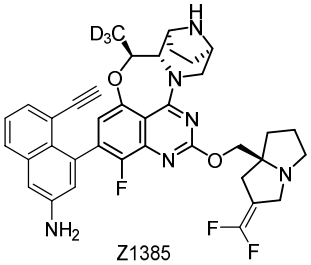

Z1060

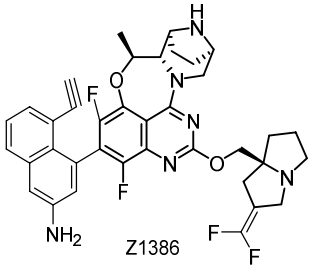

Z1054

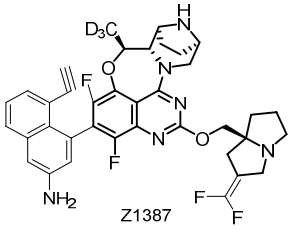

Z1072

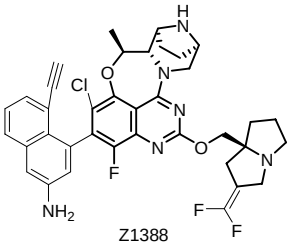

Z1295

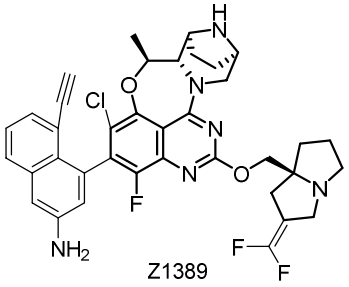

Z1384

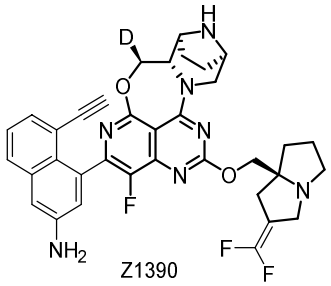

Z1385

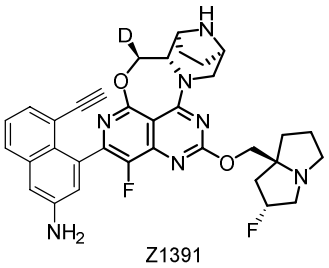

Z1386

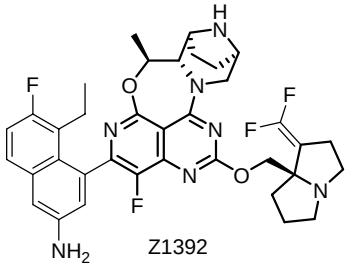

Z1387

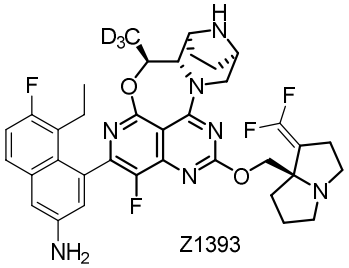

Z1388

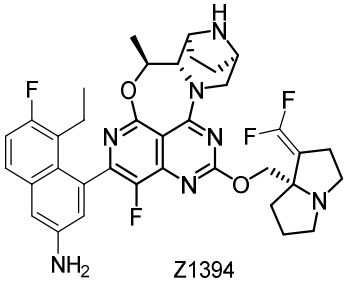

Z1389

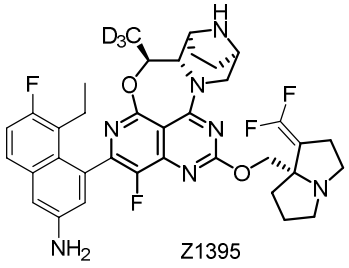

Z1390

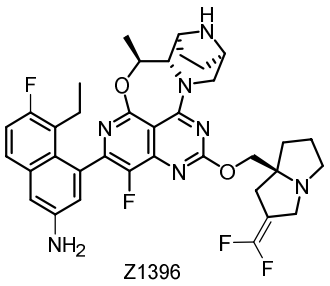

Z1391

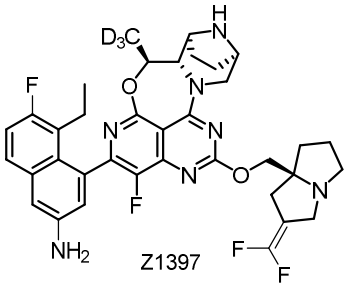

Z1392

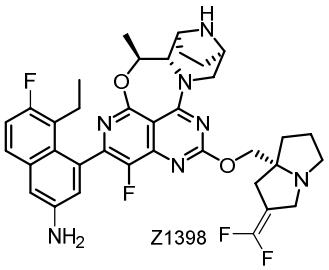

Z1393

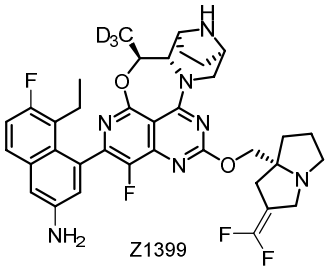

Z1394

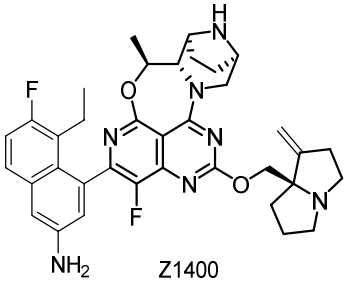

Z1395

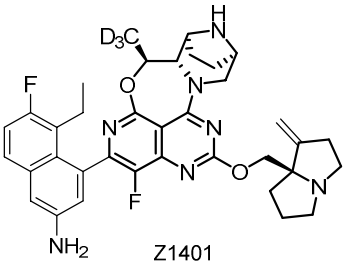

Z1396

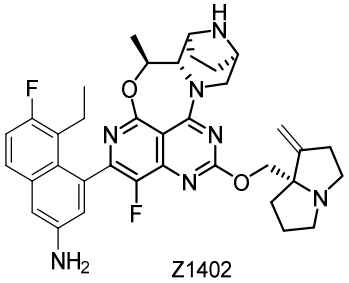

Z1397

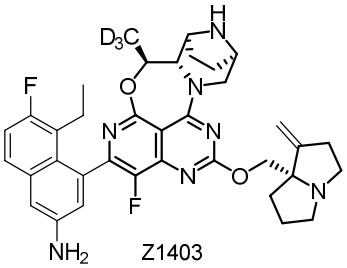

Z1398

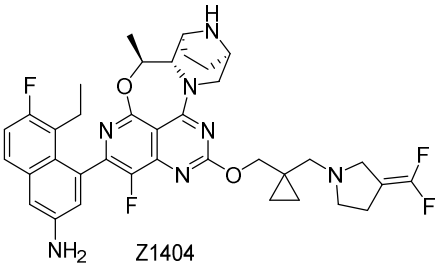

Z1399

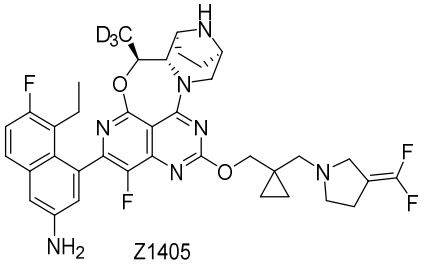

Z1400

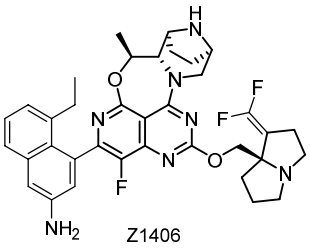

Z1401

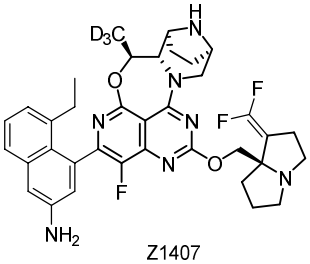

Z1402

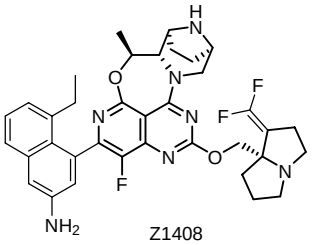

Z1403

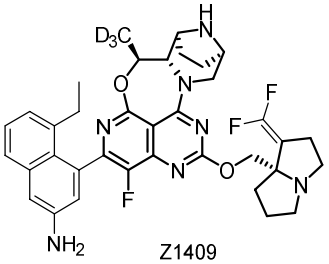

Z1404

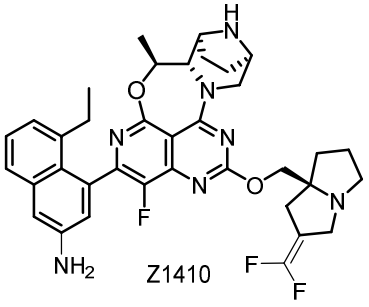

Z1405

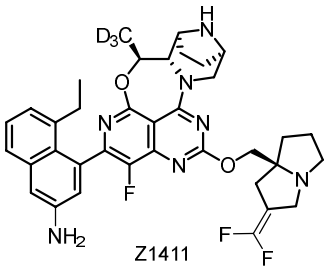

Z1406

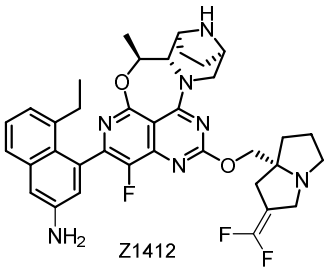

Z1407

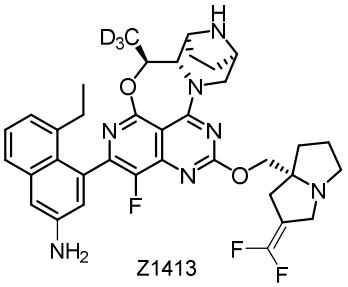

Z1408

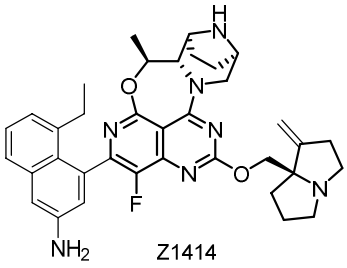

Z1409

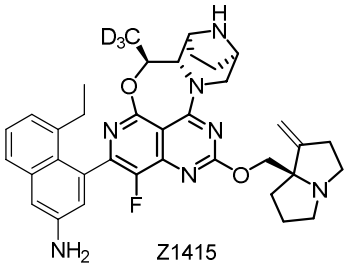

Z1410

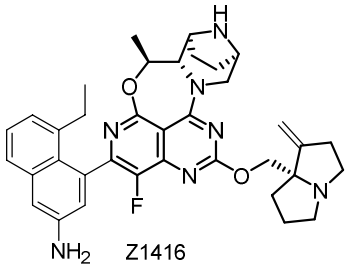

Z1411

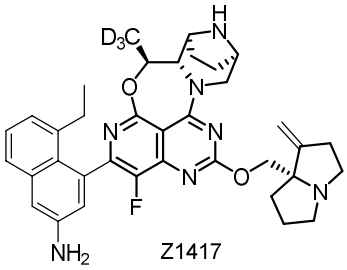

Z1412

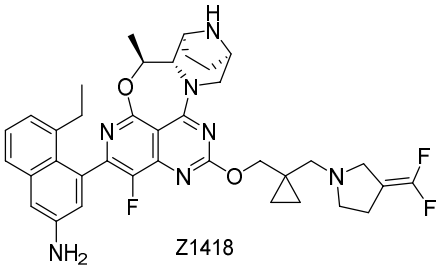

Z1413

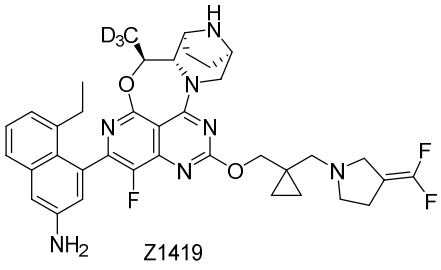

Z1414

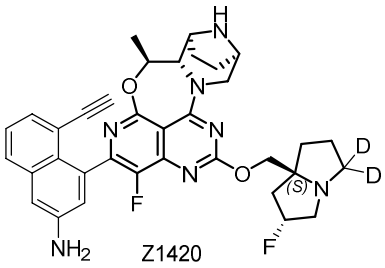

Z1415

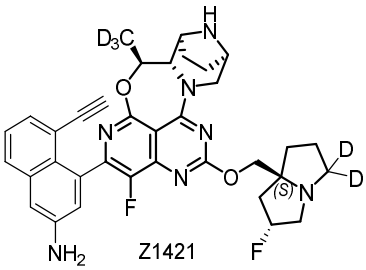

Z1416

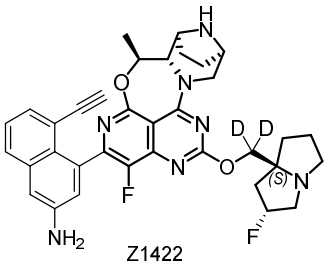

Z1417

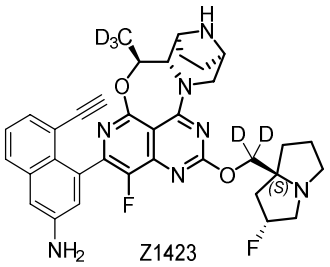

Z1418


Z1419


Z1420


Z1421


Z1422


Z1423

.

A second example of the present disclosure provides a pharmaceutical composition, which comprises the compound according to the first example or a pharmaceutically acceptable salt, stereoisomer, deuterated compound or solvate thereof, and a pharmaceutically acceptable carrier.

In one aspect, the present disclosure refers to a pharmaceutical composition, comprising a therapeutically effective amount of the compound or stereoisomer, deuterated compound, or pharmaceutically acceptable salt thereof disclosed herein; and a pharmaceutically acceptable excipient.

As used herein, the term "pharmaceutically acceptable carrier" refers to any representative carriers for preparations or carrier media, including water, oil, vegetables and minerals, paste base, lotion base, and ointment base, etc., which can deliver an effective amount of the active substance of the present disclosure without interfering with the biological activity of the active substance, and has no toxic or side effects on the host or subjects. These bases include suspending agents, tackifiers, and transdermal enhancers, etc. Their preparations are well known to those skilled in the art of cosmetics or topical medication

In an example of the present disclosure, the pharmaceutical composition can be administered through any of the following routes: oral administration, spray inhalation, rectal

administration, nasal administration, buccal administration, topical administration, parenteral administration, such as subcutaneous, intravenous, intramuscular, intraperitoneal, intrathecal, intraventricular, intrasternal and intracranial injection or infusion, or administration by means of an implanted reservoir. Among them, oral, intraperitoneal or intravenous administration is preferred. When orally administered, the compound of the present disclosure can be prepared into any form of orally acceptable preparations, including, but not limited to, tablets, capsules, aqueous solutions or aqueous suspensions. The carriers used in tablets generally include lactose and corn starch, and lubricants such as magnesium stearate can also be added. Diluents used in capsule preparations generally include lactose and dried corn starch. An aqueous suspension preparation are usually prepared by mixing an active ingredients with a suitable emulsifier and suspending agent. If needed, some sweeteners, fragrances or colorants can be added to the above oral preparations. When administered locally, particularly, to treat the affected face or organ that is easy to be reached by topical application, such as nervous diseases of eyes, skin or lower intestine, the compound of the present disclosure can be prepared into different forms of topical preparations according to different affected faces or organs. When administered locally to eyes, the compound of the present disclosure can be prepared into a preparation form of micro-suspensions or solutions, and the carrier used is isotonic sterile brine with a certain pH, in which a preservative such as a benzyl chloride alkoxide may or may not be added. For ophthalmic use, the compound can also be prepared into paste such as vaseline paste. When locally applied to the skin, the compound of the present disclosure can be prepared into an appropriate ointment, lotion or cream preparation form, in which the active ingredient is suspended or dissolved in one or more carriers. Carriers useful for ointment preparations include, but are not limited to, mineral oil, liquid vaseline, white vaseline, propylene glycol, polyethylene oxide, polypropylene oxide, emulsified wax and water. Carriers useful for lotions or creams include, but are not limited to, mineral oil, sorbitan monostearate, Tween 60, cetyl ester wax, hexadecenyl aromatic alcohol, 2- octyldodecanol, benzyl alcohol and water. The compound of the present disclosure can also be administered in the form of sterile injectable preparations, including sterile injectable aqueous or oily suspensions or sterile injectable solutions. Carriers and solvents that can be used include water, Ringer's solution and isotonic sodium chloride solution. In addition, sterilized non-volatile oil can also be used as a solvent or suspending medium, such as monoglyceride or diglyceride.

In another example, the present disclosure provides use of the compound according to the first example or a pharmaceutically acceptable salt, stereoisomer, deuterated compound or solvate thereof or the pharmaceutical composition according to the second example in the

preparation of a medicine for preventing and/or treating diseases or disorders. The diseases or disorders are KRAS G12D-related diseases or disorders.

In one aspect, the present disclosure refers to use of the compound or stereoisomer, deuterated compound, or pharmaceutically acceptable salt thereof disclosed herein, or the pharmaceutical composition disclosed herein in the manufacture of a medicament for preventing and/or treating diseases or disorders, wherein the diseases or disorders are KRAS G12D-related diseases or disorders.

As used herein, "KRAS G12D" refers to a mutant form of mammalian KRAS protein, which contains an amino acid substitution of aspartic acid for glycine at amino acid position 12. The distribution of amino acid codon and residue position of human KRAS is based on the amino acid sequence identified by UniProtKB/Swiss-Prot P01116: Variantp.Gly12Asp.

As used herein, "KRAS G12D inhibitor" refers to the compound of the present disclosure or a pharmaceutically acceptable salt, stereoisomer, deuterated compound or solvate thereof. These compounds can negatively regulate or inhibit all or part of the enzyme activity of KRAS G12D.

As used herein, "KRAS G12D-related diseases or disorders" refer to diseases or disorders related to, mediated by or having KRAS G12D mutations. Non-limiting examples of KRAS G12D-related diseases or disorders are KRAS G12D-related cancers.

Another example of the present disclosure provides a method for treating KRAS G12D-related cancers. The method includes: administering a therapeutically effective amount of the compound according to the first example of the present disclosure or a pharmaceutically acceptable salt, stereoisomer, deuterated compound or solvate thereof to a subject in need thereof; or administering a therapeutically effective amount of the pharmaceutical composition according to the second example of the present disclosure to a subject in need thereof.

Herein, in one example, the KRAS G12D-related cancers include, but are not limited to, lung cancer, prostate cancer, breast cancer, brain cancer, skin cancer, cervical cancer, testicular cancer and other tumors. In one example, the KRAS G12D-related cancers include, but are not limited to, astrocytic cancer, breast cancer, cervical cancer, colorectal cancer, endometrial cancer, esophageal cancer, gastric cancer, head and neck cancer, hepatocellular cancer, laryngeal cancer, lung cancer, oral cancer, ovarian cancer, prostate cancer, thyroid cancer, sarcoma and the like. In one example, the KRAS G12D-related cancers include, but are not limited to, cardiac cancers, such as sarcoma (angiosarcoma, fibrosarcoma, rhabdomyosarcoma, and liposarcoma), myxoma, rhabdomyoma, fibroma, lipoma and teratoma; lung cancers, for example, bronchial cancer (squamous cell, undifferentiated small cell, undifferentiated large cell, and adenocarcinoma), alveolar (bronchial) cancer, bronchial adenoma, sarcoma, lymphoma, chondromatous hamartoma, and mesothelioma; cancers of gastrointestinal tract, for example, esophagus (squamous cell carcinoma, adenocarcinoma, leiomyosarcoma, and lymphoma), stomach (carcinoma, lymphoma, and leiomyosarcoma), pancreas (ductal adenocarcinoma, insulinoma,

glucagonoma, gastrinoma, carcinoid tumor, and vipoma), small intestine (adenocarcinoma, and carcinoid tumor), Kaposi's sarcoma, leiomyoma, hemangioma, lipoma, neurofibroma, and fibroma), large intestine (adenocarcinoma, tubular adenoma, villous adenoma, hamartoma, and leiomyoma); cancers of urogenital tract, for example, kidney (adenocarcinoma, Wilms tumor (nephroblastoma), lymphoma, and leukemia), bladder and urethra (squamous cell carcinoma, transitional cell carcinoma, and adenocarcinoma), prostate (adenocarcinoma, and sarcoma), testis (seminoma, teratoma, embryonic carcinoma, and teratoma), choriocarcinoma, sarcoma, interstitial cell carcinoma, fibroma, fibroadenoma, adenomatoid tumor, and lipoma); liver cancers, for example, hepatocellular carcinoma, cholangiocarcinoma, hepatoblastoma, angiosarcoma, hepatocellular adenoma, and hemangioma; cancers of biliary tract, for example, gallbladder cancer, ampullary cancer, and cholangiocarcinoma; bone cancers, for example, osteosarcoma, fibrosarcoma, malignant fibrous histiocytoma, chondrosarcoma, Ewing's sarcoma, malignant lymphoma (reticulocytoma), multiple myeloma, malignant giant cell tumor, chordoma, osteochondroma, benign chondroma, benign osteochondroma and giant cell tumor; cancer of nervous system, for example, skull (osteoma, hemangioma, granuloma, xanthoma, and osteitis deformans), meninges (meningioma, meningosarcoma, and glioma), brain (astrocytoma, medulloblastoma, glioma, ependymoma, germ cell tumor (pineoma), glioblastoma, glioblastoma multiforme, glioblastoma, and congenital tumors), spinal neurofibroma, meningioma, glioma, and sarcoma); gynecological cancers, for example, uterus (endometrial cancer), cervix (cervical cancer, precancerous cervical dysplasia), ovary (ovarian cancer (serous cystadenocarcinoma, mucinous cystadenocarcinoma, and unclassified carcinoma), granulosa-theca cell tumor, Sertoli-Leydig cell tumor, disgerminoma, and malignant teratoma), vulva (squamous cell carcinoma, intraepithelial carcinoma, adenocarcinoma, fibrosarcoma, and melanoma), vagina (clear cell carcinoma, squamous cell carcinoma, botryoid sarcoma (embryonic rhabdomyosarcoma), fallopian tube (carcinoma); hematological cancers, for example, blood (acute and chronic myeloid leukemia), acute lymphoblastic leukemia, chronic lymphocytic leukemia, myeloproliferative diseases, multiple myeloma, myelodysplastic syndrome), Hodgkin's disease, non-Hodgkin's lymphoma (malignant lymphoma); skin cancers, for example, malignant melanoma, basal cell carcinoma, squamous cell carcinoma, Kaposi sarcoma, dysplastic nevus, lipoma, hemangioma, dermatofibroma, keloid, and psoriasis; and cancers of the adrenal gland, such as neuroblastoma.

In one example, the KRAS G12D-related cancer is lung cancer.

In one example, the KRAS G12D-related cancer is selected from the group consisting of: gastric cancer, gastric adenocarcinoma, non-small cell lung cancer, small cell lung cancer, colorectal cancer, rectal cancer or pancreatic cancer.

Another example of the present disclosure provides a method for treating a cancer in a subject in need thereof. The method includes:

(a) determining that the cancer is associated with KRAS G12D mutation (e.g., a KRAS G12D-related cancer); and

(b) administering to the subject a therapeutically effective amount of the compound according to the first example of the present disclosure or a pharmaceutically acceptable salt, stereoisomer, deuterated compound or solvate thereof; or administering to the subject a therapeutically effective amount of the pharmaceutical composition according to the second example of the present disclosure.

In one example, the administration is performed by a route selected from parenteral, intraperitoneal, intradermal, intracardiac, intraventricular, intracranial, intracerebrospinal, intracavitary, intrasynovial, intrathecal, intramuscular injection, intravitreal injection, intravenous injection, intra-arterial injection, oral, buccal, sublingual, percutaneous, local, intratracheal, rectal, subcutaneous and topical administration.

Another example of the present disclosure provides a method for inhibiting the activity of KRAS G12D in cells. The method includes: contacting the cells with the compound according to the first example of the present disclosure or a pharmaceutically acceptable salt, stereoisomer, deuterated compound or solvate thereof; or contacting the cells with the pharmaceutical composition according to the second example of the present disclosure.

Another example of the present disclosure provides use of the compound according to the first example or a pharmaceutically acceptable salt, stereoisomer, deuterated compound or solvate thereof, or the pharmaceutical composition according to the second example in the preparation of a KRAS G12D inhibitor.

As used herein, the term "subject" refers to an animal, especially a mammal, preferably, human.

As used herein, the term "effective amount" or "therapeutically effective amount" refers to a sufficient amount of a drug or medicament that is non-toxic but can achieve the desired effect. In an example of the present disclosure, when the patient is treated according to the present disclosure, the amount of a given drug depends on many factors, such as the specific dosing regimen, the type and severity of the disease or disorder, and the features (e.g., weight) of the subject or host that needs treatment. According to particular surrounding conditions, including, for example, the specific drug used, the administration route, the

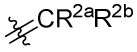
treated disorder, and the treated subject or host, the administered dosage can be determined by a method known in the art. Generally, in terms of dosage used for adult treatment, the administered dosage is typically in the range of 0.02-5000 mg/day, for example, about 1-1500 mg/day. The required dosage can be conveniently expressed as one dose, or simultaneously administered (or in a short time) or divided doses at appropriate intervals, for example, two, three, four or more doses per day. It can be understood by those skilled in the art that although the above dosage range is given, the specific effective amount can be appropriately adjusted according to the patient's condition and the doctor's determination.

As used herein, the term "pharmaceutically acceptable salt" refers to a salt of the compound of the present disclosure that is pharmaceutically acceptable and has the pharmacological activity of the parent compound. Such salts include acid addition salts with inorganic acids such as nitric acid, phosphoric acid, carbonic acid and the like; and organic acids such as propionic acid, caproic acid, cyclopentylpropionic acid, glycolic acid, pyruvic acid, gluconic acid, stearic acid, and muconic acid, etc; or salts formed when an acidic proton existing on the parent compound is replaced by a metal ion, such as an alkali metal ion or alkaline earth metal ion; or a coordination compound formed with an organic base such as ethanolamine. The pharmaceutically acceptable salt of the present disclosure can be synthesized by a conventional chemical method from the parent compound containing an acid or base radical. Generally, such a salt is prepared by reacting the compound in the form of a free acid or base with a stoichiometric amount of an appropriate base or acid in water or an organic solvent or a mixture of the two. Generally, non-aqueous media such as ether, ethyl acetate, ethanol, isopropanol or acetonitrile are preferred. In addition to the salt form, the compound provided in the present disclosure can also exist in a prodrug form. The prodrug of the compound described herein can easily undergo chemical changes under physiological conditions, thus being converted into the compound of the present disclosure. In addition, the prodrug can be chemically or biologically converted to the compound of the present disclosure in vivo.

As used herein, the term "solvate" refers to a substance formed by association of the compound of the present disclosure with a pharmaceutically acceptable solvent. The pharmaceutically acceptable solvent includes acetic acid and others. The solvate includes stoichiometric and non-stoichiometric solvates. Some compounds of the present disclosure can exist in a non-solvated form or a solvated form. Generally, the solvated form and the non-solvated form are equivalent and are both included in the scope of the present disclosure.

As used herein, the term "stereoisomer" includes conformational isomers and configurational isomers, where the configurational isomers mainly include cis-trans isomers and optical isomers. The compound of the present disclosure can exist in the form of a stereoisomer, and thus covers all possible stereoisomer forms, including, but not limited to, cis-trans isomers, tautomers, enantiomers, diastereomers, and atropisomers, etc. The compound of the present disclosure can also exist as any combination or any mixture of the aforementioned stereoisomers, for example, a mixture of equal amount of the mesomer, raceme, atropisomer, and others. For example, a single enantiomer, a single diastereomer or a mixture thereof, or a single atropisomer or a mixture thereof. When the compound of the present disclosure contains an olefin double bond, unless otherwise specified, it includes a cis isomer, a trans isomer, and any combination thereof. The atropisomer of the present disclosure is a stereoisomer with axial or planar chirality due to limited intramolecular rotation. As a drug, stereoisomers with excellent activity are preferred. The compound of the present disclosure has optical isomers derived from an asymmetric carbon, etc. If necessary, a single isomer can be obtained by resolution by methods known in the art, such as crystallization or chiral chromatography.

As used herein, the term "deuterated compound" refers to various deuterated forms of any compound disclosed in the present disclosure. Each available hydrogen atom attached to a carbon atom can be independently replaced by a deuterium atom. One of ordinary skill in the art knows how to synthesize deuterated compounds of any formula disclosed herein. For example, a deuterated material such as an alkyl group can be prepared by conventional techniques (see, for example, methyl-d3-amine, available from Aldrich Chemical Co.,Milwaukee,WI, Catalogue 489,689-2).

Herein, 2 hydrogen atoms on the same carbon atom being optionally both replaced by $=CR^{2a}R^{2b}$ means that the carbon atom is attached to a carbon atom (C) in $CR^{2a}R^{2b}$ through a double bond. That is, 2 hydrogen atoms on the same carbon atom being optionally both replaced by $=CR^{2a}R^{2b}$ means that the carbon atom is substituted with .

As used herein, when a group such as an alkyl group is located in the middle of a structural formula, the group is a ylene group. for example, the alkyl is an alkylene.

As used herein, the term "alkyl" refers to a chain-like (linear or branched) saturated aliphatic hydrocarbyl group. The term "alkyl" can be a linear or branched alkyl group (C1-20 alkyl group) containing 1 to 20 carbon atoms, preferably an alkyl group (C1-12 alkyl group) containing 1 to 12 carbon atoms. Non-limiting examples include methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, t-butyl, s-butyl, n-pentyl, 1,1-dimethylpropyl, 1,2-dimethylpropyl, 2,2-dimethylpropyl, 1-ethylpropyl, 2-methylbutyl, 3-methylbutyl, n-hexyl, 1-ethyl-2-

As used herein, the term “C1-C6 hydroxylalkyl” refers to -C1-C6 alkyl-hydroxyl(OH), preferably C1-C3 hydroxylalkyl (that is, -C1-C3 alkyl-hydroxyl) or C1-C4 hydroxylalkyl (that is, -C1-C4 alkyl-hydroxyl), where the alkyl moiety is as defined above.

As used herein, the term “C1-C6 cyanoalkyl” refes to -C1-C6 alkyl-cyano, preferably C1-C3 cyanoalkyl or C1-C4 cyanoalkyl, where the alkyl moiety is as defined above.

As used herein, the term “C2-C6 alkynyl” refers to a linear and branched aliphatic group having 2-6 carbon atoms and 1 or 2 carbon-carbon triple bond, preferably C2-C4 alkynyl or C2-C3 alkynyl. Examples of alkynyl include, but are not limited to, ethynyl, propynyl, and butynyl.

As used herein, the term “C2-C6 haloalkynyl” means that one or more hydrogen in C2-C6 alkynyl is replaced by halogen, where the alkynyl moiety is as defined above. C2-C3 haloalkynyl or C2-C4 haloalkynyl is preferred. Examples of haloalkynyl include, but are not limited to, monofluoroethynyl and difluoroethynyl.

As used herein, the term “C2-C6 alkenyl” refers to a linear and branched aliphatic group having 2-6 carbon atoms and 1 or 2 carbon-carbon double bond, preferably C2-C4 alkenyl or C2-C3 alkenyl. Examples of alkenyl include, but are not limited to, ethenyl, propenyl, and butenyl.

As used herein, the term “C2-C6 haloalkenyl” means that one or more hydrogen in C2-C6 alkenyl is replaced by halogen, where the alkenyl moiety is as defined above. C2-C3 haloalkenyl or C2-C4 haloalkenyl is preferred. Examples of haloalkenyl include, but are not limited to, monofluoroethenyl, and difluoroethenyl.

As used herein, the term “C2-C6 hydroxyalkynyl” refers to -C2-C6 alkynyl-OH, where the alkynyl is as defined above. C2-C4 hydroxyalkynyl or C2-C3 hydroxyalkynyl is preferred.

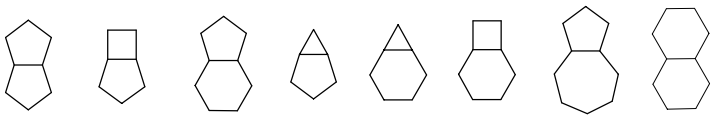
As used herein, the term “C2-C6 hydroxyalkenyl” refres to -C2-C6 alkenyl-OH, where the alkenyl is as defined above. C2-C4hydroxyalkenyl or C2-C3hydroxyalkenyl is preferred.

As used herein, the term “C1-C4 alkylene” refers to a C1-C4 alkyl as defined above, which is located between the other two parts of the molecule and is used to connect them. Typical alkylene include, but are not limited to, methylene, ethylene, propylene and butylene.

In the present disclosure, the above-mentioned alkyl, alkenyl and alkynyl can be optionally substituted, and when substituted, the substituent group is preferably one or more substituent groups described in the present application.

As used herein, the term “cycloalkyl” and “cycloalkyl ring” are used interchangeably and refer to a saturated monocyclic or polycyclic hydrocarbyl group, for example, monocyclic cycloalkyl, spiro cycloalkyl, fused cycloalkyl, and bridged cycloalkyl. In the present disclosure, the ring carbon atoms of the cycloalkyl can be substituted with 1,2 or 3 oxo groups to form

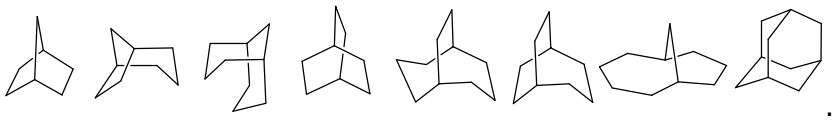
is C8 (C5 monocyclic cycloalkyl ring fused with C5 monocyclic cycloalkyl ring), C9 (C5 monocyclic cycloalkyl ring fused with C6 monocyclic cycloalkyl ring) or C10 (C6 monocyclic cycloalkyl ring fused with C6 monocyclic cycloalkyl ring) bicyclic fused cycloalkyl. Specific examples of fused cycloalkyl include, but are not limited to:



.

These fused cycloalkyl groups can be attached to the rest of the molecule through any ring atom.

As used herein, the term “bridged cycloalkyl” and “bridged cycloalkyl ring” refer to a polycyclic hydrocarbyl group formed by sharing two carbon atoms that are not directly connected by two or more monocyclic rings. According to the number of rings contained, it can be divided into bicyclic, tricyclic, tetracyclic or polycyclic bridged cycloalkyl. The term “C5-C20 bridged cycloalkyl” refers to a polycyclic hydrocarbyl with 5 to 20 ring carbon atoms, in which any two rings share two carbon atoms that are not directly connected. C6-C14 bridged cycloalkyl is preferred. C7-C10 bridged cycloalkyl is further preferred. Specific examples of bridged cycloalkyl include, but are not limited to:



.

These bridged cycloalkyl groups can be attached to the rest of the molecule through any ring atom.

For example, examples of cycloalkyl herein include, but are not limited to, cyclopropyl, cyclobutyl, cyclopentyl, cyclopentenyl, cyclohexyl, cyclohexenyl, cycloheptyl, cyclooctyl, bicyclo[1.1.1]pentyl.

As used herein, the term “cycloalkoxy” refers to -O- cycloalkyl, in which the cycloalkyl is as defined above.

In the present disclosure, the above-mentioned cycloalkyl can be optionally substituted, and when substituted, the substituent group is preferably one or more substituent groups described in the present application.

As used herein, the term “heterocyclyl” and “heterocyclyl ring” are used interchangeably and refer to a saturated or partially unsaturated monocyclic or polycyclic hydrocarbyl, for example, monocyclic heterocyclyl, spiroheterocyclyl, fused heterocyclyl, and bridged heterocyclyl. In the present disclosure, the ring carbon atom of the heterocyclyl can be substituted with 1, 2 or 3 oxo groups to form a cyclic ketone, cyclic lactone or cyclic lactam structure. For example, , the term “3- to 20-membered heterocyclyl” refers to a saturated or

partially unsaturated monocyclic or polycyclic hydrocarbyl group with 3 to 20 ring atoms, in which one or more (preferred is 1,2, 3 or 4) ring atoms is selected from heteroatoms such as nitrogen, oxygen, or $S(=O)_{m'}$ (where m' is an integer from 0 to 2), but excluding the ring moiety of -O-O-, -O-S- or -S-S-; and the rest ring atoms are carbon. When the ring atom is a nitrogen atom, it may be substituted or unsubstituted (i.e., N or NR, in which R is hydrogen or other substituents as defined herein). In the present disclosure, the 3- to 20-membered heterocyclyl includes monocyclic heterocyclyl (for example, 3- to 8-membered monocyclic heterocyclyl), 5- to 20-membered spiro heterocyclyl, 5- to 20-membered fused heterocyclyl, and 5- to 20-membered bridged heterocyclyl.

As used herein, the term “3- to 20-membered nitrogen containing heterocyclyl” refers to a saturated or partially unsaturated monocyclic hydrocarbyl with 3 to 20 ring atoms containing at least 1 nitrogen atom. The group is attached to the rest of the molecule through the nitrogen atom. The group also optionally contains additional 1 or 2 heteroatoms selected from nitrogen, oxygen or $S(=O)_{m'}$ (where m' is an integer from 0 to 2) as a ring atom. In the present disclosure, the 3- to 20-membered nitrogen containing heterocyclyl includes a monocyclic heterocyclyl (for example, 3- to 8-membered monocyclic nitrogen containing heterocyclyl), 5- to 20-membered nitrogen containing spiroheterocyclyl, 5- to 20-membered nitrogen containing fused heterocyclyl, and 5- to 20-membered nitrogen containing bridged heterocyclyl.

As used herein, the term “3- to 8-membered monocyclic heterocyclyl” and “3- to 8-membered monocyclic heterocyclyl ring” refers to a saturated or partially unsaturated monocyclic hydrocarbyl group with 3 to 8 ring atoms, in which 1, 2 or 3 ring atoms are heteroatoms selected from nitrogen, oxygen or $S(=O)_{m'}$ (where m' is an integer from 0 to 2). The group is preferably a 3- to 6-membered monocyclic heterocyclyl having 3 to 6 ring atoms, in which 1 or 2 ring atoms are heteroatoms. The group is further preferably a 4- to 6-membered monocyclic heterocyclyl having 4 to 6 ring atoms, in which 1 or 2 ring atoms are heteroatoms. The group is preferably a 5- or 6-membered monocyclic heterocyclyl having 5 or 6 ring atoms, in which 1 or 2 ring atoms are heteroatoms. When the heteroatom is a nitrogen atom, the nitrogen atom may be substituted or unsubstituted (i.e., N or NR, in which R is hydrogen or other substituents as defined herein). When the heteroatom is a sulfur atom, the sulfur atom may be optionally oxidized (that is, $S(=O)_{m'}$, in which m' is an integer from 0 to 2). The ring carbon atom of the monocyclic heterocyclyl may be optionally substituted with 1, 2 or 3 oxo groups to form a cycloketone, cyclolactone or cyclolactam structure. Specific examples of monocyclic heterocyclyl include, but are not limited to, aziridine, ethylene oxide, azetidine, azetidin-2-one, oxetane, oxetan-2-one, oxazolidine,

The group is attached to the rest of the molecule through the nitrogen atom; and the group optionally contains additional 1 or 2 or 3 heteroatoms selected from nitrogen, oxygen, or $S(=O)_{m'}$ (where m' is an integer from 0 to 2) as a ring atom.

In the present disclosure, the above-mentioned heterocyclyl can be optionally substituted, and when substituted, the substituent group is preferably one or more substituent groups described in the present application.

Specifically, in the present disclosure, specific examples of the heterocyclyl include, but are not limited to, epoxy, azetidinyl, tetrahydrofuranyl, tetrahydropyranyl, pyrrolidinyl, pyrrolidinonyl, piperidinyl, piperazinyl, imidazolyl, imidazopyridinyl, thiazolyl, oxazolidinyl, oxazolidinonyl, decahydrogenquinolinyl, piperidinonyl, morpholinyl, azabicyclohexyl, azabicycloheptyl, azabicyclooctyl, azabicyclononyl, azabicyclodecyl, azaspiroheptyl, azaspirooctyl, azaspirononyl, azaspirodecyl, tetrahydrospiro[cyclopropane-1,2'-pyrrolizin]yl, hexahydro-1H-pyrrolizinyl, hexahydro-1H-pyrrolo[2,1-c][1,4]oxazinyl, octahydroindolizinyl, oxaspiroheptyl, oxaspirooctyl, oxaspirononyl, oxaspirodecyl, diazaspirononyl, oxabicyclohexyl, oxabicycloheptyl, oxabicyclooctyl, and hexahydroalloxazin4(1H)-oxide.

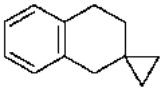
As used herein, the term "aryl" refers to an all-carbon monocyclic, all-carbon non-fused polycyclic (the rings are connected by a covalent bond, and not fused) or all-carbon fused polycyclic (i.e., rings sharing an adjacent pair of carbon atoms) group, in which at least one ring is aromatic, i.e., has a conjugated π electron system. For example, the term “C6-C14 aryl” refers to an aryl having 6 to 14 ring atoms. C6-C10 aryl is preferred. In the present disclosure, the C6-C14 aryl includes monocyclic aryl, non-fused polycyclic aryl, and aromatic fused polycyclic aryl. Examples of monocyclic aryl include phenyl, and examples of non-fused polycyclic aryl include biphenylyl.

In the present disclosure, when C6-C14 aryl is an aromatic fused polycyclic aryl, the aromatic fused polycyclic aryl may be a polycyclic group formed by fusing a monoaryl ring with one or more monaryl rings, and non-limiting examples thereof include naphthyl, anthracenyl and the like.

In some examples of the present disclosure, when the C6-C14 aryl is an aromatic fused polycyclic ring, the aromatic fused polycyclic ring may also be a polycyclic group formed by fusing a monoaryl ring (such as phenyl) with one or more nonaromatic rings, where the ring connected to the parent structure is an aromatic ring or nonaromatic ring. The nonaromatic ring includes, but is not limited to, a 3- to 6-membered monocyclic heterocyclyl ring (preferably, a 5- or 6-membered monocyclic heterocyclyl ring, where the ring carbon atom in the monocyclic heterocyclyl ring can be substituted with 1 to 2 oxo groups to form a cyclolactam or cyclolactone structure), a 3- to 6-membered monocyclic

cycloalkyl ring (preferably a 5- or 6-membered monocyclic cycloalkyl ring, where the ring carbon atom in the monocyclic cycloalkyl ring can be substituted with 1 or 2 oxo groups to form a cycloketone structure). The polycyclic group in which the monoaryl ring is fused with one or more nonaromatic rings can be connected to other groups or the parent structure through the nitrogen atom or carbon atom, and the ring connected to the parent structure is a monoaryl ring or a nonaromatic ring.

In the present disclosure, the above-mentioned aryl can be substituted or unsubstituted, and when substituted, the substituent group is preferably one or more substituent groups described in the present application.

As used herein, the term “aryl” refers to a C6-C14 aromatic group having 1 to 3 aromatic rings. It can be optionally substituted with one or more (e.g. 1, 2, 3, 4 or 5) R^6 or one or more (for example, 1, 2, 3, 4 or 5) R^7. In an example, the aryl is C6-C10 aryl. Examples of the aryl include, but are not limited to, phenyl, naphthalenyl, anthracenyl, fluorenyl, and dihydrobenzofuranyl. The "aryl" also refers to a bicyclic or tricyclic system, where one or two rings in the aryl group may be saturated or partially saturated, respectively. If the aryl group contains two saturated rings, the two saturated rings may form a fused ring system or a spiro ring system. Examples of the aryl containing two saturated rings (and a spiro ring system) include .

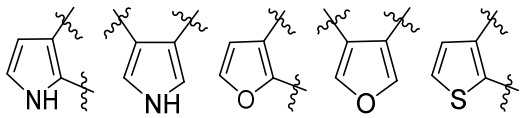
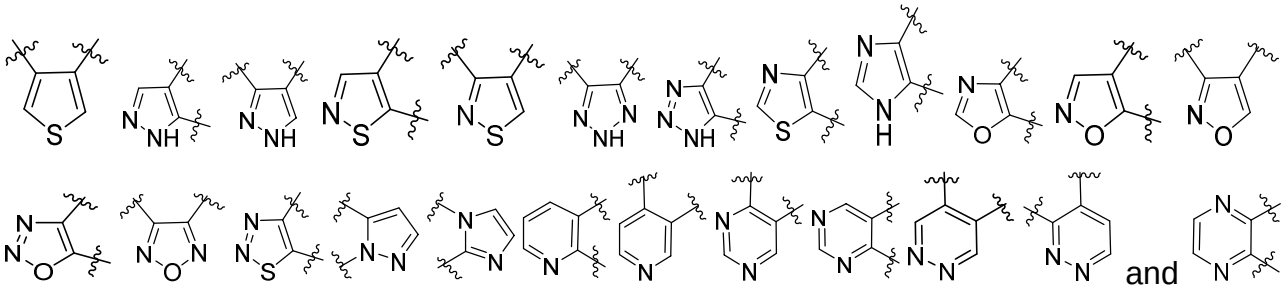
As used herein, the term “aryl-C1-C6 alkyl” or “aralkyl” is meant to include an aryl group covalently attached to an alkyl group. The aryl is as defined above, the alkyl is as defined above, and either or both of the aryl and alkyl can be independently optionally substituted or unsubstituted. An example of the aralkyl is (C6-C10) aryl (C1-C6) alkyl-. Specific examples include, but are not limited to, benzyl, phenylethyl and naphthylmethyl. An example of a substituted aryl-C1-C6 alkyl is one in which the alkyl is substituted by hydroxyalkyl.

As used herein, the term “heteroaryl” refers to a monocyclic or fused polycyclic (i.e., sharing an adjacent pair of ring atoms, which can be C-C or N-C) group in which the ring atom is replaced by at least one heteroatom independently selected from nitrogen, oxygen or sulfur, where the nitrogen and sulfur atom can be optionally oxidized, and the nitrogen atom can be optionally quaternized. The heteroaryl has shared 6, 10 or 14 π electrons, and at least one ring in the group is aromatic. For example, the term “5- to 14-membered heteroaryl” refers to a heteroaryl having 5 to 14 ring atoms, in which 1, 2, 3 or 4 ring atoms are heteroatoms selected from nitrogen, oxygen or $S(=O)_{m'}$ (where m' is an integer from 0 to 2). The group is preferably a 5- to 10-membered heteroaryl having 5 to 10 ring atoms, in

which 1, 2, 3 or 4 ring atoms are heteroatoms. In the present disclosure, the 5- to 14-membered heteroaryl may be a monocyclic heteroaryl (for example, a 5- or 6-membered monocyclic heteroaryl), a fused bicyclic heteroaryl (for example, a 8- to 10-membered bicyclic heteroaryl) or a fused tricyclic heteroaryl.

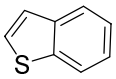
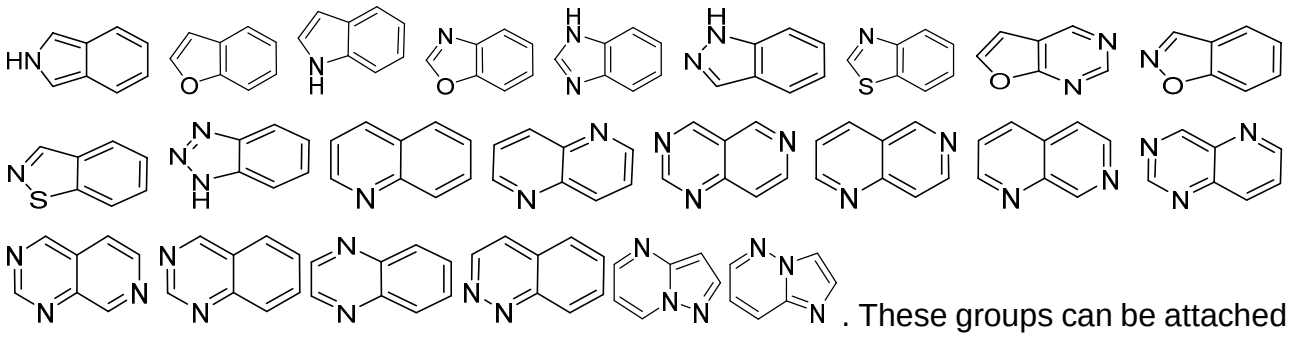
As used herein, the term “5- or 6-membered monocyclic heteroaryl” refers to a monocyclic heteroaryl having 5 or 6 ring atoms, where 1, 2 or 3 ring atoms are heteroatoms selected from nitrogen, oxygen or $S(=O)_{m'}$ (where m' is an integer from 0 to 2). Specific examples of the monocyclic heteroaryl include, but are not limited to, thiophene, furan, thiazole, isothiazole, imidazole, oxazole, pyrrole, pyrazole, triazole, 1,2,3-triazole, 1,2,4-triazole, 1,2,5-triazole, 1,3,4-triazole, tetrazole, isooxazole, oxadiazole, 1,2,3-oxadiazole, 1,2,4-oxadiazole, 1,2,5-oxadiazole, 1,3,4-oxadiazole, thiadiazole, pyridine, pyridazine, pyrimidine, and pyrazine.

As used herein, the term “8 to 10-membered bicyclic heteroaryl” refers to a fused bicyclic heteroaryl having 8 to 10 ring atoms, in which 1, 2, 3, 4 or 5 ring atoms are heteroatoms selected from nitrogen, oxygen or $S(=O)_{m'}$ (where m' is an integer from 0 to 2). The fused bicyclic heteroaryl can be a bicyclic group (preferably a 9 or 10-membered bicyclic heteroaryl ring) formed by fusing a monoaryl ring (such as phenyl) with a monocyclic heteroaryl ring (preferably a 5- or 6-membered monocyclic heteroaryl ring), or a bicyclic group formed by fusing a monocyclic heteroaryl ring (preferably a 5- or 6-membered monocyclic heteroaryl ring) with a monocyclic heteroaryl ring (preferably 5- or 6-membered monocyclic heteroaryl ring).

Any 2 ring atoms connected on the monocyclic heteroaryl ring, including C-C, N-C and N-N, can be fused with a cycloalkyl, heterocyclyl, aryl or heteroaryl such as a monocyclic cycloalkyl ring, a monocyclic heterocyclyl ring, a monoaryl ring, and a 5- or 6-membered monocyclic heteroaryl ring as defined herein, to form a fused polycyclic ring. The 2 ring atoms connected on the monocyclic heteroaryl ring that form a fused ring with other rings are preferably C-C, including, without limitation,   and .

The ring atom marked with “ ” in the above groups is attached to the rest of the molecule.

Non-limiting examples of the 8- to 10-membered bicyclic heteroaryl include: benzo[d]isoxazole, 1H-indole, isoindole, 1H-benzo[d]imidazole, benzo[d]isothiazole, 1H-benzo[d][1,2,3]triazole, benzo[d]oxazole, benzo[d]thiazole, indazole, benzofuran, benzo[b]thiophene, quinoline, isoquinoline, quinazoline, quinoxaline, cinnoline, pyrido[3,2-d]pyrimidine, pyrido[2,3-d]pyrimidine, pyrido[3,4-d]pyrimidine, pyrido[4,3-d]pyrimidine, 1,8-naphthyridine, 1,7-naphthyridine, 1,6-naphthyridine, 1,5-naphthyridine, pyrazolo[1,5-a]pyrimidine, and imidazo[1,2-b]pyridazine.

Specific examples of bicyclic heteroaryl include, but are not limited to:   . These groups can be attached to the rest of the molecule through any suitable ring atom. The ring connected to the parent structure can be a monocyclic heteroaryl ring or a benzene ring.

In some examples of the present disclosure, the fused bicyclic heteroaryl or fused tricyclic cycloheteroaryl may be a polycyclic group formed by fusing a monocyclic heteroaryl ring (preferably a 5- or 6-membered monocyclic heteroaryl ring) with one or more nonaromatic rings, where the ring connected to the parent structure is a monocyclic heteroaryl ring or nonaromatic ring. The nonaromatic ring includes, but is not limited to, a 3- to 6-membered monocyclic heterocyclyl ring (preferably, a 5- or 6-membered monocyclic heterocyclyl ring, where the ring carbon atom in the monocyclic heterocyclyl ring can be substituted with 1 to 2 oxo groups to form a cyclolactam or cyclolactone structure), a 3- to 6-membered monocyclic cycloalkyl ring (preferably a 5- or 6-membered monocyclic cycloalkyl ring, where the ring carbon atom in the monocyclic cycloalkyl ring can be substituted with 1 or 2 oxo groups to form a cycloketone structure). The polycyclic group formed by fusing the monocyclic heteroaryl ring is fused with one or more nonaromatic rings can be connected to other groups or the parent structure through the nitrogen atom or carbon atom, and the ring connected to the parent structure is a monocyclic heteroaryl ring or a nonaromatic ring.

In the present disclosure, the above-mentioned heteroaryl can be substituted or unsubstituted, and when substituted, the substituent group is preferably one or more substituent groups described in the present application.

As used herein, the term “acetyl” refers to -C(O)CH_3.

As used herein, the term “halo” refers to fluoro, chloro, bromo, and iodo.

Unless otherwise specified, the structure described in the present disclosure further includes a compound having one or more isotope-enriched atoms. Exemplary isotopes that can be incorporated into the compound of the present disclosure include isotopes of hydrogen, carbon, nitrogen, oxygen, phosphorus, sulfur, fluoro, chloro, chloro and iodo, for example, 2H, 3H, 11C, 13C, 14C, 13N, 15N, 15O, 17O, 18O, 32P, 33P, 35S, 18F, 36Cl, 123I, and 125I.

BRIEF DESCRIPTION OF THE DRAWINGS

Fig. 1 is a three-dimensional structural diagram showing a molecule of Compound B obtained by single crystal diffraction.

DETAILED DESCRIPTION

The compound of the present invention can be prepared by a variety of synthesis methods well known to those skilled in the art, including the specific embodiments listed below, the embodiments formed by the combination of the listed synthesis methods with other chemical synthesis methods, and equivalent alternatives well-known to those skilled in the art. Preferred embodiments include, but are not limited to, examples of the present invention. Herein, some of the synthesis methods of the intermediates or starting compounds are shown in preparation examples, and some are shown a certain example. If the same intermediate or starting compound is used in the remaining examples, the preparation of this compound will not be described repeatedly.

The present invention will be described in detail by way of examples, these examples do not imply any adverse limitation to the present invention. The present invention is described in detail herein, and the specific embodiments thereof are also disclosed. It will be obvious for those skilled in the art to make various changes and improvements to the specific embodiments of the present invention without departing from the spirit and scope of the present invention. Where no specific conditions are given in the examples, conventional conditions or conditions recommended by the manufacturer are followed. The reagents or instruments for which no manufacturers are noted are all common products commercially available from the market.

For example, a compound of Formula (A-4) can be prepared in the following manner.