immune responses, including an activation of the NFkB pathway and increased TNF-alpha production in dendritic cells of patients with Crohn's disease.

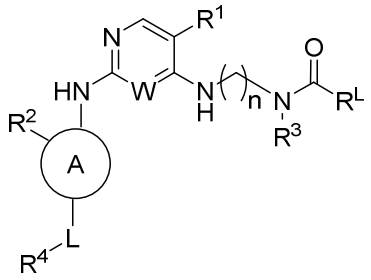
[00010] Inhibitors of LRRK2 are sought for the treatment of neurodegenerative diseases including Parkinson's disease, and also are sought for the treatment of gastrointestinal diseases including Crohn's disease, ulcerative colitis, and inflammatory bowel disease.

[00011] There is a need for new targeted therapies which inhibit autophagy and can be used in combination with MAPKAP pathway inhibitors, chemotherapeutic agents, and/or other targeted therapeutics.

SUMMARY

[00012] Described herein are compounds that are inhibitors of autophagy, pharmaceutical compositions, and their use as agents in the treatment of disorders such as cancer, processes for their preparation, and pharmaceutical compositions containing them as an active ingredient. Such pharmaceutical compositions may comprise the compound as the sole active agent or in combination with other active agents in the presence of a pharmaceutically acceptable excipient. In an ~~embodiment~~example, the described compounds are inhibitors of ULK kinase activity, including ULK1 and ULK2 activity.

[00012a] In one aspect of the present disclosure, there is provided A compound represented by:



Formula I

or a pharmaceutically acceptable salt, enantiomer, stereoisomer, or tautomer thereof, wherein:

A is selected from the group consisting of phenyl and a 5 or 6-membered heteroaryl;

W is CH or N;

R^1 is selected from the group consisting of halogen, cyano, C_1-C_5alkyl, and C_3-C_5cycloalkyl, wherein C_1-C_5alkyl and C_3-C_5cycloalkyl may be optionally substituted by one, two or three independent occurrences of fluorine;

R^2 is selected from the group consisting of halogen, cyano, C_1-C_5alkyl, C_3-C_6cycloalkyl, C_2-C_5alkenyl, C_2-C_5alkynyl, C_1-C_5alkoxy, and C_1-C_5alkoxy-C_2-C_5alkyl, wherein each C_1-C_5alkyl, C_3-C_6cycloalkyl, C_2-C_5alkenyl, C_2-C_5alkynyl, and C_1-C_5alkoxy may be optionally substituted by one, two, or three independent occurrences of fluorine or cyano;

R^3 is selected from the group consisting of H, C_1-C_3alkyl, and C_3-C_5cycloalkyl, wherein C_1-C_3alkyl and C_3-C_5cycloalkyl may be optionally substituted by one or more independent occurrences of fluorine;

R^4 is selected from the group consisting of B, D, NR^6R^9, NR^6-$(C(R^{10})_2)_p$-NR^6R^9, C(O)-NR^6R^9; C(O)-B; C(O)-D , and CN;

B is selected from an N-linked heterocyclyl having at least one nitrogen and optionally having an additional ring nitrogen or oxygen and heteroaryl, wherein B may be optionally substituted on one or more available carbons by R^7 and may be optionally substituted on an available nitrogen by R^9;

D is selected from a C-linked heterocyclyl having at least one nitrogen and optionally having an additional ring nitrogen or oxygen and heteroaryl, wherein D may be optionally substituted on one or more available carbons by R^7 and may be optionally substituted on an available nitrogen by R^9;

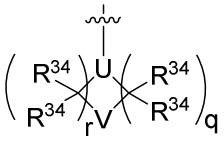
each occurrence of R^7 is independently selected from the group consisting of H, C_1-C_6alkyl, C_3-C_6cycloalkyl, cyano, and $(C(R^{10})_2)_h$-NR^6R^9, wherein C_1-C_6alkyl and C_3-C_6cycloalkyl may be optionally substituted by one or more independent occurrences of fluorine, or two R^7 are joined together with the atom to which they are attached to form oxo;

R^6 is selected from the group consisting of H, C_1-C_6alkyl, C_3-C_6cycloalkyl, C_1-C_5alkoxy-C_2-C_5alkyl, C(=O)R^5, SO_2R^5, C-linked heterocyclyl having at least one nitrogen and optionally having an additional ring nitrogen or oxygen, and heteroaryl, wherein C_1-C_6alkyl and C_3-C_6cycloalkyl may be optionally substituted by one or more independent occurrences of fluorine;

R^9 is selected from the group consisting of H, C_1-C_6alkyl, C_3-C_6cycloalkyl, C_1-C_5alkoxy-C_2-C_5alkyl, C(=O)R^5, SO_2R^5, C-linked heterocyclyl having at least one nitrogen and optionally having an additional ring nitrogen or oxygen, and heteroaryl, wherein C_1-C_6alkyl and C_3-C_6cycloalkyl may be optionally substituted by one or more independent occurrences of fluorine;

R^5 is selected from the group consisting of H, C_1-C_6alkyl, C_3-C_6cycloalkyl, and heterocyclyl, wherein C_1-C_6alkyl and C_3-C_6cycloalkyl may be optionally substituted by one or more independent occurrences of fluorine;

each occurrence of R^{10} is independently selected from the group consisting of H, C_1-C_3alkyl, and C_3-C_5cycloalkyl, wherein C_1-C_3alkyl and C_3-C_5cycloalkyl may be optionally substituted by one or more independent occurrences of fluorine, or two R^{10} are joined together with the carbon to which they are attached to form a C_3-C_5cycloalkyl;

R^L is selected from the group consisting of C_1-C_6alkyl and C_3-C_6cycloalkyl, $NR^{11}R^{12}$, and 

, wherein each C_1-C_6alkyl and C_3-C_6cycloalkyl may be optionally substituted by 1, 2, or 3 independent occurrences of fluorine;

U is N or CR^{13};

V is selected from the group consisting of oxygen, $C(R^{34})_2$, and NR^6;

r is 0, 1, or 2;

q is 1, 2, or 3;

R^{11} is selected from the group consisting of H, C_1-C_3alkyl, and C_3-C_5cycloalkyl, wherein C_1-C_3alkyl and C_3-C_5cycloalkyl may be optionally substituted by one or more independent occurrences of fluorine;

R^{12} is selected from the group consisting of H, C_1-C_3alkyl, and C_3-C_5cycloalkyl, wherein C_1-C_3alkyl and C_3-C_5cycloalkyl may be optionally substituted by one or more independent occurrences of fluorine;

R^{13} is selected from H and C_1-C_3alkyl;

each occurrence of R^{34} is independently selected from H, C_1-C_3alkyl, and C_3-C_5cycloalkyl, wherein C_1-C_3alkyl and C_3-C_5cycloalkyl may be optionally substituted by one or more independent occurrences of fluorine, or two R^{34} are joined together with the carbon to which they are attached to form a C_3-C_6cycloalkyl;

L is $-(C(R^{10})_2)_m-$;

h is 1, 2, or 3;

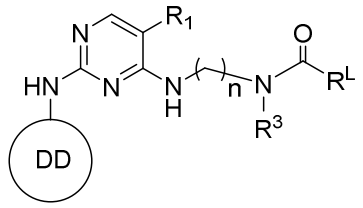
m is 0, 1, 2, or 3;

n is 2, 3, or 4; and

p is 2 or 3;

provided that when m is 0, R^4 is C-linked to ring A, when m is 1, R^4 is C-linked to L, and when m is 2 or 3, R^4 is N-linked or C-linked to L; and further provided that when r is 0 and q is 1, then U is not CR^{13} and V is not O, and when r or q is 1, then U is not N and V is not O or NR^6.

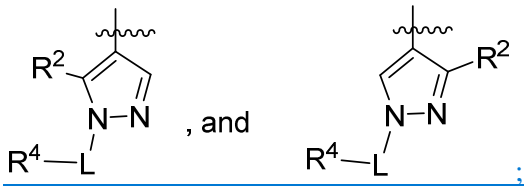
[00012b] In another aspect of the present disclosure, there is provided a compound represented by:



Formula IE

or a pharmaceutically acceptable salt thereof, wherein:

ring DD is selected from the group consisting of:



;

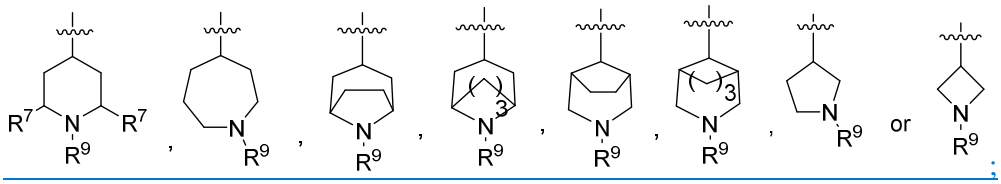
n is 2, 3, or 4;

R^1 is selected from the group consisting of halogen, cyano, C_1-C_5alkyl, and C_3-C_5cycloalkyl, wherein C_1-C_5alkyl and C_3-C_5cycloalkyl may be optionally substituted by one, two or three independent occurrences of fluorine;

R^2 is selected from the group consisting of C_1-C_2alkyl and C_3-C_4cycloalkyl, and halogen, wherein C_1-C_2alkyl and C_3-C_4cycloalkyl may be optionally substituted by one, two or three independent occurrences of fluorine;

R^3 is selected from the group consisting of H, C_1-C_3alkyl, and C_3-C_5cycloalkyl, wherein C_1-C_3alkyl and C_3-C_5cycloalkyl may be optionally substituted by one or more independent occurrences of fluorine;

R^4 is selected from the group consisting of:

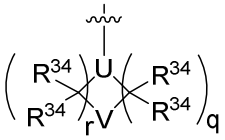


;

R^9 is selected from the group consisting of H, C_1-C_6alkyl, C_3-C_6cycloalkyl, $C(=O)R^5$, SO_2R^5, C-linked heterocyclyl having at least one nitrogen and optionally having an additional ring nitrogen or oxygen and heteroaryl, wherein C_1-C_6alkyl and C_3-C_6cycloalkyl may be optionally substituted by one or more independent occurrences of fluorine;

R^5 is selected from the group consisting of H, C_1-C_6alkyl, C_3-C_6cycloalkyl, and heterocyclyl, wherein C_1-C_6alkyl and C_3-C_6cycloalkyl may be optionally substituted by one or more independent occurrences of fluorine;

each occurrence of R^7 is independently selected from the group consisting of H, C_1-C_6 alkyl, and C_3-C_6cycloalkyl, wherein C_1-C_6alkyl and C_3-C_6cycloalkyl may be optionally substituted by one or more independent occurrences of fluorine, or two R^7 are joined together with the atom to which they are attached to form oxo;

R^L is selected from the group consisting of C_1-C_6alkyl and C_3-C_6cycloalkyl, $NR^{11}R^{12}$, and 

, wherein each C_1-C_6alkyl and C_3-C_6cycloalkyl may be optionally substituted by 1, 2, or 3 independent occurrences of fluorine;

U is N or CR^{13};

V is selected from the group consisting of oxygen, $C(R^{34})_2$, and NR^6;

r is 0, 1, or 2;

q is 1, 2, or 3;

R^6 is selected from the group consisting of H, C_1-C_6alkyl, C_3-C_6cycloalkyl, $C(=O)R^5$, SO_2R^5, C-linked heterocyclyl having at least one nitrogen and optionally having an additional ring nitrogen or oxygen and heteroaryl, wherein C_1-C_6alkyl and C_3-C_6cycloalkyl may be optionally substituted by one or more independent occurrences of fluorine;

R^{11} is selected from the group consisting of H, C_1-C_3alkyl, and C_3-C_5cycloalkyl, wherein C_1-C_3alkyl and C_3-C_5cycloalkyl may be optionally substituted by one or more independent occurrences of fluorine;

R^{12} is selected from the group consisting of H, C_1-C_3alkyl, and C_3-C_5cycloalkyl, wherein C_1-C_3alkyl and C_3-C_5cycloalkyl may be optionally substituted by one or more independent occurrences of fluorine;

R^{13} is selected from H and C_1-C_3alkyl;

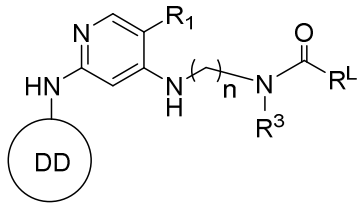
each occurrence of R^{34} is independently selected from H, C_1-C_3alkyl, and C_3-C_5cycloalkyl, wherein C_1-C_3alkyl and C_3-C_5cycloalkyl may be optionally substituted by one or more independent occurrences of fluorine, or two R^{34} are joined together with the carbon to which they are attached to form a C_3-C_6cycloalkyl; and

L is $-(C(R^{10})_2)_m-$;

m is 0, 1, 2, or 3;

provided that when m is 0, R4 is C-linked to the pyrazolyl ring, when m is 1, R^4 is C-linked to L, and when m is 2 or 3, R^4 is N-linked or C-linked to L; and further provided that when r is 0 and q is 1, then U is not CR^{13} and V is not O, and when r or q is 1, then U is not N and V is not O or NR^6.

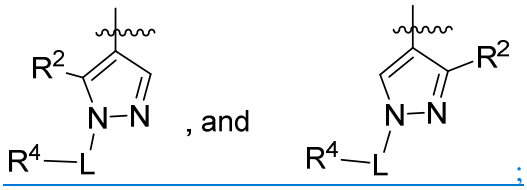
[00012c] In a further aspect of the present disclosure, there is provided a compound represented by:



Formula IF

or a pharmaceutically acceptable salt thereof, wherein:

ring DD is selected from the group consisting of:



;

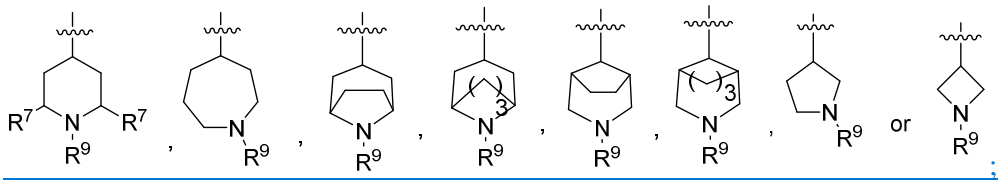
n is 2, 3, or 4;

R^1 is selected from the group consisting of halogen, cyano, C_1-C_5alkyl, and C_3-C_5cycloalkyl, wherein C_1-C_5alkyl and C_3-C_5cycloalkyl may be optionally substituted by one, two or three independent occurrences of fluorine;

R^2 is selected from the group consisting of C_1-C_2alkyl and C_3-C_4cycloalkyl, and halogen, wherein C_1-C_2alkyl and C_3-C_4cycloalkyl may be optionally substituted by one, two or three independent occurrences of fluorine;

R^3 is selected from the group consisting of H, C_1-C_3alkyl, and C_3-C_5cycloalkyl, wherein C_1-C_3alkyl and C_3-C_5cycloalkyl may be optionally substituted by one or more independent occurrences of fluorine;

R^4 is selected from the group consisting of:

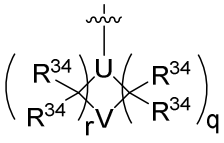


;

R^9 is selected from the group consisting of H, C_1-C_6alkyl, C_3-C_6cycloalkyl, $C(=O)R^5$, SO_2R^5, C-linked heterocyclyl having at least one nitrogen and optionally having an additional ring nitrogen or oxygen and heteroaryl, wherein C_1-C_6alkyl and C_3-C_6cycloalkyl may be optionally substituted by one or more independent occurrences of fluorine;

R^5 is selected from the group consisting of H, C_1-C_6alkyl, C_3-C_6cycloalkyl, and heterocyclyl, wherein C_1-C_6alkyl and C_3-C_6cycloalkyl may be optionally substituted by one or more independent occurrences of fluorine;

each occurrence of R^7 is independently selected from the group consisting of H, C_1-C_6 alkyl, and C_3-C_6cycloalkyl, wherein C_1-C_6alkyl and C_3-C_6cycloalkyl may be optionally substituted by one or more independent occurrences of fluorine, or two R^7 are joined together with the atom to which they are attached to form oxo;

R^L is selected from the group consisting of C_1-C_6alkyl and C_3-C_6cycloalkyl, $NR^{11}R^{12}$, and , wherein each C_1-C_6alkyl and C_3-C_6cycloalkyl may be optionally substituted by 1, 2, or 3 independent occurrences of fluorine;

U is N or CR^{13};

V is selected from the group consisting of oxygen, $C(R^{34})_2$, and NR^6;

r is 0, 1, or 2;

q is 1, 2, or 3;

R^6 is selected from the group consisting of H, C_1-C_6alkyl, C_3-C_6cycloalkyl, $C(=O)R^5$, SO_2R^5, C-linked heterocyclyl having at least one nitrogen and optionally having an additional

ring nitrogen or oxygen and heteroaryl, wherein C_1-C_6alkyl and C_3-C_6cycloalkyl may be optionally substituted by one or more independent occurrences of fluorine;

R^{11} is selected from the group consisting of H, C_1-C_3alkyl, and C_3-C_5cycloalkyl, wherein C_1-C_3alkyl and C_3-C_5cycloalkyl may be optionally substituted by one or more independent occurrences of fluorine;

R^{12} is selected from the group consisting of H, C_1-C_3alkyl, and C_3-C_5cycloalkyl, wherein C_1-C_3alkyl and C_3-C_5cycloalkyl may be optionally substituted by one or more independent occurrences of fluorine;

R^{13} is selected from H and C_1-C_3alkyl;

each occurrence of R^{34} is independently selected from H, C_1-C_3alkyl, and C_3-C_5cycloalkyl, wherein C_1-C_3alkyl and C_3-C_5cycloalkyl may be optionally substituted by one or more independent occurrences of fluorine, or two R^{34} are joined together with the carbon to which they are attached to form a C_3-C_6cycloalkyl; and

L is $-(C(R^{10})_2)_m-$;

m is 0, 1, 2, or 3;

provided that when m is 0, R4 is C-linked to the pyrazolyl ring, when m is 1, R4 is C-linked to L, and when m is 2 or 3, R4 is N-linked or C-linked to L; and further provided that when r is 0 and q is 1, then U is not CR^{13} and V is not O, and when r or q is 1, then U is not N and V is not O or NR^6.

[00012d] In another aspect of the present disclosure, there is provided a pharmaceutical composition comprising a compound disclosed herein and a pharmaceutically acceptable excipient.

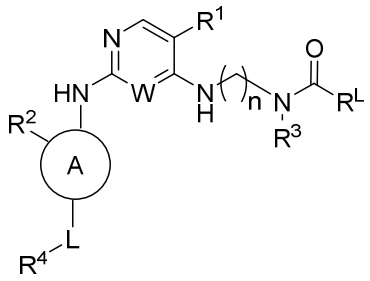
[00012e] In a further aspect of the present disclosure, there is provided a pharmaceutical composition comprising a compound disclosed herein, one or more additional therapeutic agents, and a pharmaceutically acceptable excipient.

[00012f] In another aspect of the present disclosure, there is provided a use of a compound disclosed herein in the manufacture of a medicament for treating a tumor in a patient in need thereof.

[00012g] In a further aspect of the present disclosure, there is provided a use of a compound disclosed hereinin the manufacture of a medicament for treating a cancer in a patient in need thereof.

[00012h] In another aspect of the present disclosure, there is provided a compound disclosed herein for use in therapy.

[00013] For example, compounds provided herein may be described by Formula I:

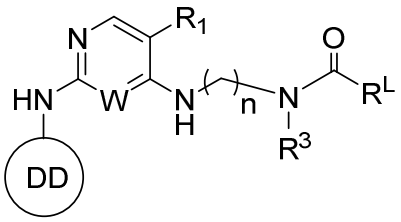


Formula I

or a pharmaceutically acceptable salt, enantiomer, stereoisomer, or tautomer thereof, wherein: A is selected from the group consisting of phenyl and a 5 or 6-member or heteroaryl; W is CH or N; R^1 is selected from the group consisting of halogen, cyano, C_1-C_5alkyl, and C_3-C_5cycloalkyl, wherein C_1-C_5alkyl and C_3-C_5cycloalkyl may be optionally substituted by one, two or three independent occurrences of fluorine; R^2 is selected from the group consisting of halogen, cyano, C_1-C_5alkyl, C_3-C_6cycloalkyl, C_2-C_5alkenyl, C_2-C_5alkynyl, C_1-C_5alkoxy, and C_1-C_5alkoxy-C_2-C_5alkyl, wherein each C_1-C_5alkyl, C_3-C_6cycloalkyl, C_2-C_5alkenyl, C_2-C_5alkynyl, and C_1-C_5alkoxy may be optionally substituted by one, two, or three independent occurrences of fluorine or cyano; R^3 is selected from the group consisting of H, C_1-C_3alkyl,

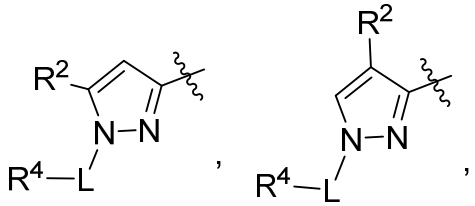
and C_3-C_5cycloalkyl, wherein C_1-C_3alkyl and C_3-C_5cycloalkyl may be optionally substituted by one or more independent occurrences of fluorine; R^{12} is selected from the group consisting of H, C_1-C_3alkyl, and C_3-C_5cycloalkyl, wherein C_1-C_3alkyl and C_3-C_5cycloalkyl may be optionally substituted by one or more independent occurrences of fluorine; R^{13} is selected from H and C_1-C_3alkyl; each occurrence of R^{34} is independently selected from H, C_1-C_3alkyl, and C_3-C_5cycloalkyl, wherein C_1-C_3alkyl and C_3-C_5cycloalkyl may be optionally substituted by one or more independent occurrences of fluorine, or two R^{34} are joined together with the carbon to which they are attached to form a C_3-C_6cycloalkyl; L is $-(C(R^{10})_2)_m-$; h is 1, 2, or 3; m is 0, 1, 2, or 3; n is 2, 3, or 4; and p is 2 or 3; provided that both of X and Y are not N, when r is 0 and q is 1, then U is not CR^{13} and V is not O, and when r or q is 1, then U is not N and V is not O or NR^6.

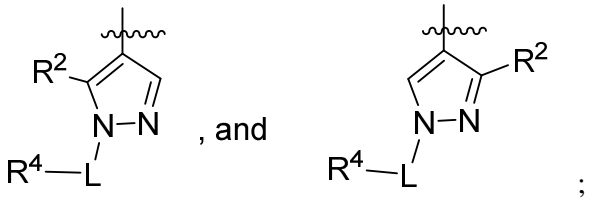
[00015] In a further ~~aspect~~example, described herein is a compound of Formula ID



Formula ID

or a pharmaceutically acceptable salt, enantiomer, stereoisomer, or tautomer thereof, wherein: ring DD is selected from the group consisting of



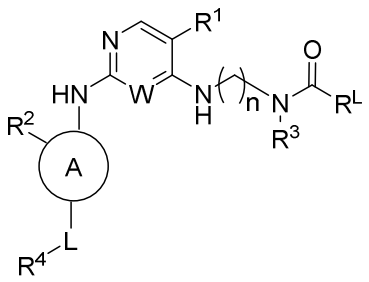


W is CH or N; R^1 is selected from the group consisting of halogen, cyano, C_1-C_5alkyl, and C_3-C_5cycloalkyl, wherein C_1-C_5alkyl and C_3-C_5cycloalkyl may be optionally substituted by one, two or three independent occurrences of fluorine; R^2 is selected from the group consisting of halogen, cyano, C_1-C_5alkyl, C_3-C_6cycloalkyl, C_2-C_5alkenyl, C_2-C_5alkynyl, C_1-

CLAIMS

What is claimed is:

1. A compound represented by:



Formula I

or a pharmaceutically acceptable salt, enantiomer, stereoisomer, or tautomer thereof, wherein:

A is selected from the group consisting of phenyl and a 5 or 6-membered ~~or~~ heteroaryl;

W is CH or N;

R^1 is selected from the group consisting of halogen, cyano, C_1-C_5alkyl, and C_3-C_5cycloalkyl, wherein C_1-C_5alkyl and C_3-C_5cycloalkyl may be optionally substituted by one, two or three independent occurrences of fluorine;

R^2 is selected from the group consisting of halogen, cyano, C_1-C_5alkyl, C_3-C_6cycloalkyl, C_2-C_5alkenyl, C_2-C_5alkynyl, C_1-C_5alkoxy, and C_1-C_5alkoxy-C_2-C_5alkyl, wherein each C_1-C_5alkyl, C_3-C_6cycloalkyl, C_2-C_5alkenyl, C_2-C_5alkynyl, and C_1-C_5alkoxy may be optionally substituted by one, two, or three independent occurrences of fluorine or cyano;

R^3 is selected from the group consisting of H, C_1-C_3alkyl, and C_3-C_5cycloalkyl, wherein C_1-C_3alkyl and C_3-C_5cycloalkyl may be optionally substituted by one or more independent occurrences of fluorine;

R^4 is selected from the group consisting of B, D, NR^6R^9, NR^6-$(C(R^{10})_2)_p$-NR^6R^9, C(O)-NR^6R^9; C(O)-B; C(O)-D , and CN;

B is selected from an N-linked heterocyclyl having at least one nitrogen and optionally having an additional ring nitrogen or oxygen and heteroaryl, wherein B may be optionally substituted on one or more available carbons by R^7 and may be optionally substituted on an available nitrogen by R^9;

D is selected from a C-linked heterocyclyl having at least one nitrogen and optionally having an additional ring nitrogen or oxygen and heteroaryl, wherein D may be optionally

substituted on one or more available carbons by R^7 and may be optionally substituted on an available nitrogen by R^9;

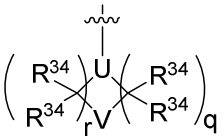
each occurrence of R^7 is independently selected from the group consisting of H, C_1-C_6alkyl, C_3-C_6cycloalkyl, cyano, and $(C(R^{10})_2)_h$-NR^6R^9, wherein C_1-C_6alkyl and C_3-C_6cycloalkyl may be optionally substituted by one or more independent occurrences of fluorine, or two R^7 are joined together with the atom to which they are attached to form oxo;

R^6 is selected from the group consisting of H, C_1-C_6alkyl, C_3-C_6cycloalkyl, C_1-C_5alkoxy-C_2-C_5alkyl, $C(=O)R^5$, SO_2R^5, C-linked heterocyclyl having at least one nitrogen and optionally having an additional ring nitrogen or oxygen, and heteroaryl, wherein C_1-C_6alkyl and C_3-C_6cycloalkyl may be optionally substituted by one or more independent occurrences of fluorine;

R^9 is selected from the group consisting of H, C_1-C_6alkyl, C_3-C_6cycloalkyl, C_1-C_5alkoxy-C_2-C_5alkyl, $C(=O)R^5$, SO_2R^5, C-linked heterocyclyl having at least one nitrogen and optionally having an additional ring nitrogen or oxygen, and heteroaryl, wherein C_1-C_6alkyl and C_3-C_6cycloalkyl may be optionally substituted by one or more independent occurrences of fluorine;

R^5 is selected from the group consisting of H, C_1-C_6alkyl, C_3-C_6cycloalkyl, and heterocyclyl, wherein C_1-C_6alkyl and C_3-C_6cycloalkyl may be optionally substituted by one or more independent occurrences of fluorine;

each occurrence of R^{10} is independently selected from the group consisting of H, C_1-C_3alkyl, and C_3-C_5cycloalkyl, wherein C_1-C_3alkyl and C_3-C_5cycloalkyl may be optionally substituted by one or more independent occurrences of fluorine, or two R^{10} are joined together with the carbon to which they are attached to form a C_3-C_5cycloalkyl;

R^L is selected from the group consisting of C_1-C_6alkyl and C_3-C_6cycloalkyl, $NR^{11}R^{12}$, and , wherein each C_1-C_6alkyl and C_3-C_6cycloalkyl may be optionally substituted by 1, 2, or 3 independent occurrences of fluorine;

U is N or CR^{13};

V is selected from the group consisting of oxygen, $C(R^{34})_2$, and NR^6;

r is 0, 1, or 2;

q is 1, 2, or 3;

R^{11} is selected from the group consisting of H, C_1-C_3alkyl, and C_3-C_5cycloalkyl, wherein C_1-C_3alkyl and C_3-C_5cycloalkyl may be optionally substituted by one or more independent occurrences of fluorine;

R^{12} is selected from the group consisting of H, C_1-C_3alkyl, and C_3-C_5cycloalkyl, wherein C_1-C_3alkyl and C_3-C_5cycloalkyl may be optionally substituted by one or more independent occurrences of fluorine;

R^{13} is selected from H and C_1-C_3alkyl;

each occurrence of R^{34} is independently selected from H, C_1-C_3alkyl, and C_3-C_5cycloalkyl, wherein C_1-C_3alkyl and C_3-C_5cycloalkyl may be optionally substituted by one or more independent occurrences of fluorine, or two R^{34} are joined together with the carbon to which they are attached to form a C_3-C_6cycloalkyl;

L is $-(C(R^{10})_2)_m-$;

h is 1, 2, or 3;

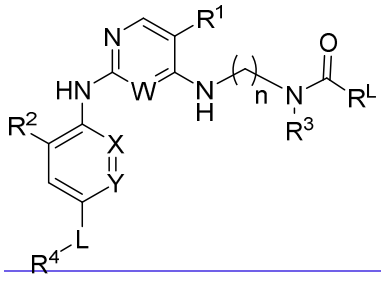
m is 0, 1, 2, or 3;

n is 2, 3, or 4; and

p is 2 or 3;

provided that when m is 0, R^4 is C-linked to ring A, when m is 1, R^4 is C-linked to L, and when m is 2 or 3, R^4 is N-linked or C-linked to L; and further provided that when r is 0 and q is 1, then U is not CR^{13} and V is not O, and when r or q is 1, then U is not N and V is not O or NR^6.

~~2. A compound represented by:~~



~~**Formula IA**~~

~~or a pharmaceutically acceptable salt, enantiomer, stereoisomer, or tautomer thereof, wherein:~~

~~W is CH or N;~~

~~X is CH or N;~~

~~Y is $C(R^{33})$ or N;~~

R^1 is selected from the group consisting of halogen, cyano, C_1-C_5alkyl, and C_3-C_5cycloalkyl, wherein C_1-C_5alkyl and C_3-C_5cycloalkyl may be optionally substituted by one, two or three independent occurrences of fluorine;

R^2 is selected from the group consisting of halogen, cyano, C_1-C_5alkyl, C_3-C_6cycloalkyl, C_2-C_5alkenyl, C_2-C_5alkynyl, C_1-C_5alkoxy, and C_1-C_5alkoxy-C_2-C_5alkyl, wherein each C_1-C_5alkyl, C_3-C_6cycloalkyl, C_2-C_5alkenyl, C_2-C_5alkynyl, and C_1-C_5alkoxy may be optionally substituted by one, two, or three independent occurrences of fluorine or cyano;

R^3 is selected from the group consisting of H, C_1-C_3alkyl, and C_3-C_5cycloalkyl, wherein C_1-C_3alkyl and C_3-C_5cycloalkyl may be optionally substituted by one or more independent occurrences of fluorine;

R^{33} is selected from the group consisting of H, halogen, C_1-C_6alkyl, and C_1-C_6alkoxy, wherein C_1-C_6alkyl and C_1-C_6alkoxy may be optionally substituted by one or more independent occurrences of fluorine;

R^4 is selected from the group consisting of B, D, NR^6R^9, NR^6-$(C(R^{10})_2)_p$-NR^6R^9, $C(O)$-NR^6R^9; $C(O)$-B; $C(O)$-D , and CN;

B is selected from an N-linked heterocyclyl having at least one nitrogen and optionally having an additional ring nitrogen or oxygen and heteroaryl, wherein B may be optionally substituted on one or more available carbons by R^7 and may be optionally substituted on an available nitrogen by R^9;

D is selected from a C-linked heterocyclyl having at least one nitrogen and optionally having an additional ring nitrogen or oxygen and heteroaryl, wherein D may be optionally substituted on one or more available carbons by R^7 and may be optionally substituted on an available nitrogen by R^9;

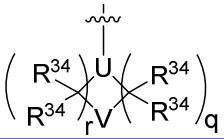
each occurrence of R^7 is independently selected from the group consisting of H, C_1-C_6alkyl, C_3-C_6cycloalkyl, cyano, and $(C(R^{10})_2)_h$-NR^6R^9, wherein C_1-C_6alkyl and C_3-C_6cycloalkyl may be optionally substituted by one or more independent occurrences of fluorine, or two R^7 are joined together with the atom to which they are attached to form oxo;

R^6 is selected from the group consisting of H, C_1-C_6alkyl, C_3-C_6cycloalkyl, C_1-C_5alkoxy-C_2-C_5alkyl, $C(=O)R^5$, SO_2R^5, C-linked heterocyclyl having at least one nitrogen and optionally having an additional ring nitrogen or oxygen, and heteroaryl, wherein C_1-C_6alkyl and C_3-C_6cycloalkyl may be optionally substituted by one or more independent occurrences of fluorine;

R^9 is selected from the group consisting of H, C_1-C_6alkyl, C_3-C_6cycloalkyl, C_1-C_5alkoxy-C_2-C_5alkyl, $C(=O)R^5$, SO_2R^5, C-linked heterocyclyl having at least one nitrogen and optionally having an additional ring nitrogen or oxygen, and heteroaryl, wherein C_1-C_6alkyl and C_3-C_6cycloalkyl may be optionally substituted by one or more independent occurrences of fluorine;

R^5 is selected from the group consisting of H, C_1-C_6alkyl, C_3-C_6cycloalkyl, and heterocyclyl, wherein C_1-C_6alkyl and C_3-C_6cycloalkyl may be optionally substituted by one or more independent occurrences of fluorine;

each occurrence of R^{10} is independently selected from the group consisting of H, C_1-C_3alkyl, and C_3-C_5cycloalkyl, wherein C_1-C_3alkyl and C_3-C_5cycloalkyl may be optionally substituted by one or more independent occurrences of fluorine, or two R^{10} are joined together with the carbon to which they are attached to form a C_3-C_5cycloalkyl;

R^L is selected from the group consisting of C_1-C_6alkyl and C_3-C_6cycloalkyl, $NR^{11}R^{12}$, and 

, wherein each C_1-C_6alkyl and C_3-C_6cycloalkyl may be optionally substituted by 1, 2, or 3 independent occurrences of fluorine;

U is N or CR^{13};

V is selected from the group consisting of oxygen, $C(R^{34})_2$, and NR^6;

r is 0, 1, or 2;

q is 1, 2, or 3;

R^{11} is selected from the group consisting of H, C_1-C_3alkyl, and C_3-C_5cycloalkyl, wherein C_1-C_3alkyl and C_3-C_5cycloalkyl may be optionally substituted by one or more independent occurrences of fluorine;

R^{12} is selected from the group consisting of H, C_1-C_3alkyl, and C_3-C_5cycloalkyl, wherein C_1-C_3alkyl and C_3-C_5cycloalkyl may be optionally substituted by one or more independent occurrences of fluorine;

R^{13} is selected from H and C_1-C_3alkyl;

each occurrence of R^{34} is independently selected from H, C_1-C_3alkyl, and C_3-C_5cycloalkyl, wherein C_1-C_3alkyl and C_3-C_5cycloalkyl may be optionally substituted by one or more independent occurrences of fluorine, or two R^{34} are joined together with the carbon to which they are attached to form a C_3-C_6cycloalkyl;

L is $-(C(R^{10})_2)_m-$;

~~h is 1, 2, or 3;~~

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

~~n is 2, 3, or 4; and~~

~~p is 2 or 3;~~

~~provided that both of X and Y are not N, when r is 0 and q is 1, then U is not CR^{13} and V is not O, and when r or q is 1, then U is not N and V is not O or NR^{6}.~~

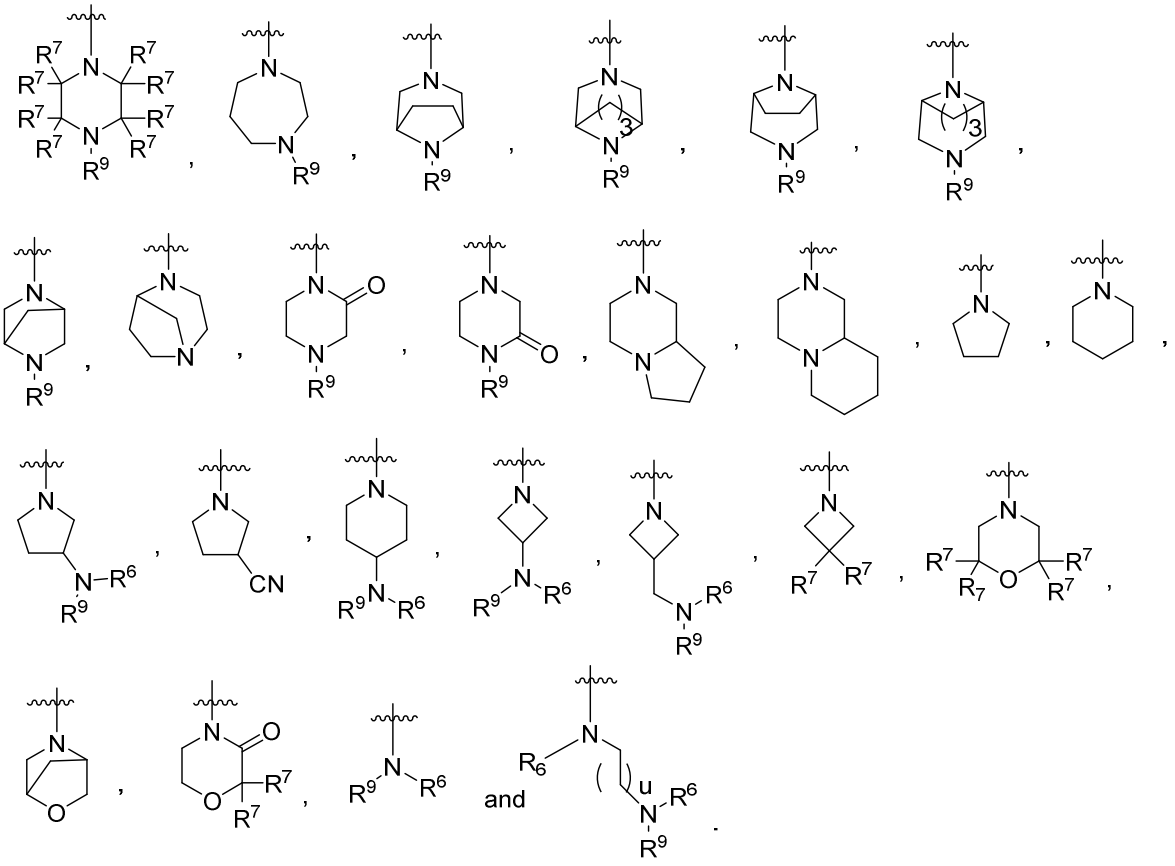
~~3. The compound of claim 1 or claim 2, wherein W is N.~~

~~4. The compound of any one of claims 1-3, wherein X is CH and Y is N.~~

~~5. The compound of any one of claims 1-3, wherein X is CH and Y is $C(R^{33})$.~~

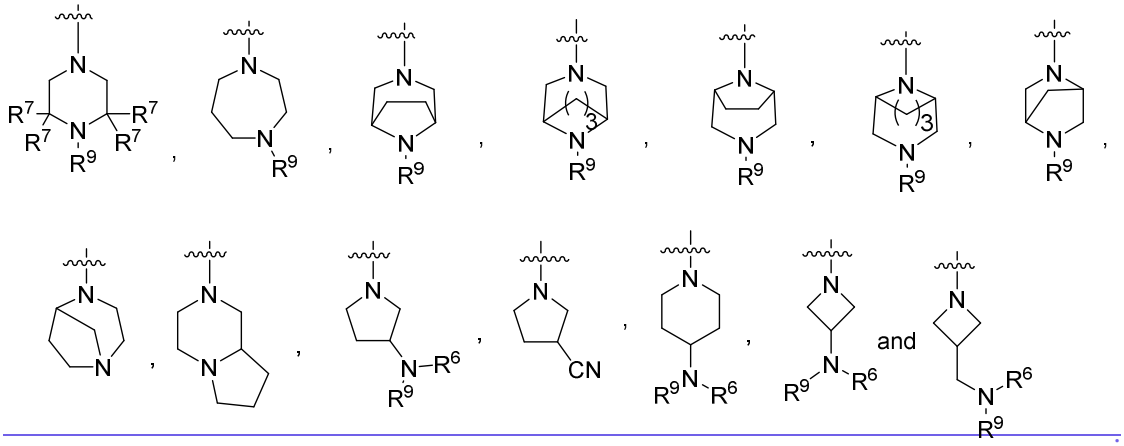
~~6. The compound of any one of claims 1-5, wherein R^4 is B.~~

~~7~~2. The compound of ~~any one of claims~~claim 1~~-6~~, wherein R^4 is selected from the group consisting of:

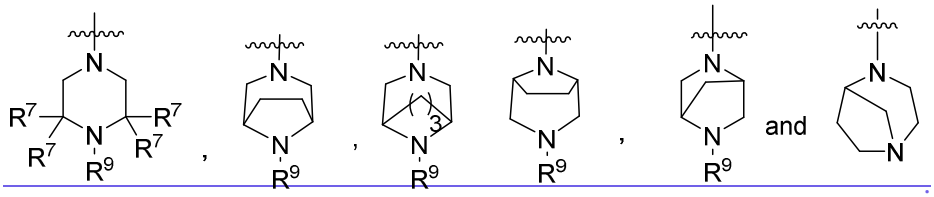


wherein u is 1, 2, or 3.

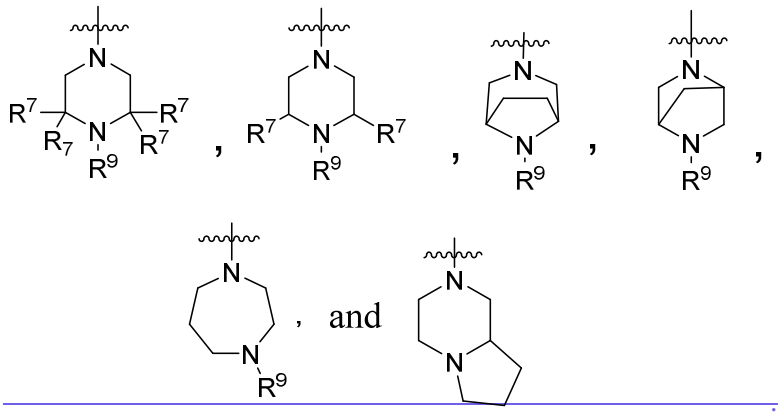
~~8. The compound of any one of claims 1-7, wherein R^4 is selected from the group consisting of:~~



~~9. The compound of any one of claims 1-8, wherein R^4 is selected from the group consisting of:~~

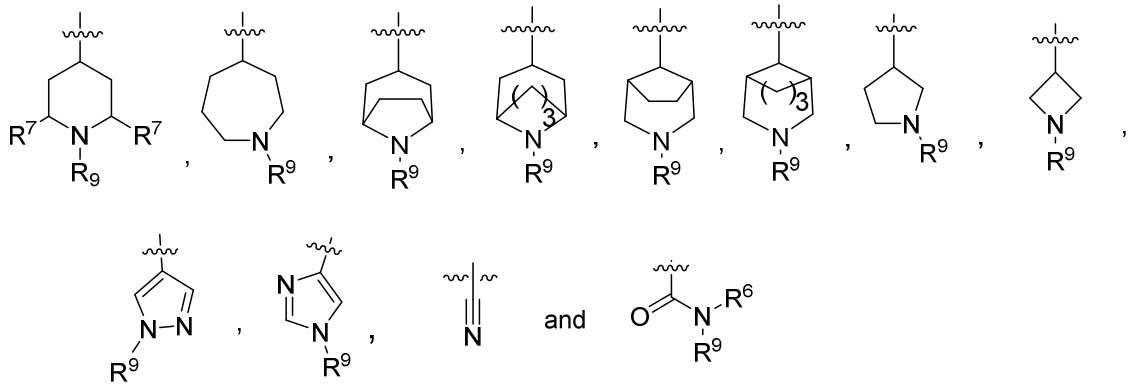


~~10. The compound of any one of claims 1-7, wherein R^4 is selected from the group consisting of:~~



~~11. The compound of any one of claims 1-5, wherein R^4 is D.~~

~~123~~. The compound of ~~any one of claims 1-5 or claim 11~~claim 1, wherein R^4 is selected from the group consisting of:



.

~~13. The compound of any one of claims 1-12, wherein L is -$(CH_2)_m$-.~~

~~14. The compound of any one of claims 1-13, wherein m is 0.~~

~~4~~15. The compound of any one of claims 1-~~14~~3, wherein R^1 is selected from the group consisting of halogen, C_1-C_5alkyl, and C_3-C_5cycloalkyl, wherein C_1-C_5alkyl and C_3-C_5cycloalkyl may be optionally substituted with one, two, or three independent occurrences of fluorine.

~~16. The compound of any one of claims 1-15, wherein R^1 is CF_3.~~

~~17. The compound of any one of claims 1-15, wherein R^1 is CF_2H.~~

~~18. The compound of any one of claims 1-15, wherein R^1 is selected from the group consisting of chloro, bromo, and fluoro.~~

~~19. The compound of claim 18, wherein R^1 is bromo.~~

~~20. The compound of any one of claims 1-15, wherein R^1 is cyclopropyl.~~

~~2~~15. The compound of any one of claims 1-~~20~~4, wherein R^2 is selected from the group consisting of C_3-C_5cycloalkyl, C_1-C_5alkyl, halogen, CN, C_2-C_5alkenyl, and C_2-C_5alknyl,

wherein C_3-C_5cycloalkyl, C_1-C_5alkyl, C_2-C_5alkenyl, and C_2-C_5alknyl may be optionally substituted with one, two, or three independent occurrences of fluorine.

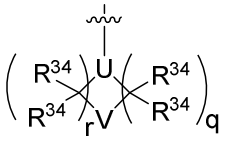
~~22. The compound of any one of claims 1-21, wherein R^2 is selected from the group consisting of C_{1-2}alkyl and C_{3-4}cycloalkyl.~~

623. The compound of any one of claims 1-225, wherein R^3 is selected ~~form~~ from the group consisting of H and C_1-C_3alkyl, wherein C_1-C_3alkyl may be optionally substituted by one or more independent occurrences of fluorine.

247. The compound of any one of claims 1-236, wherein R^L is selected from the group consisting of C_1-C_6alkyl and C_3-C_6cycloalkyl, each of which may be optionally substituted by 1, 2, or 3 independent occurrences of fluorine.

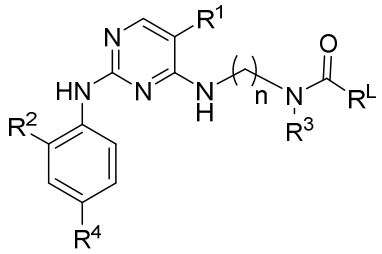
~~25. The compound of any one of claims 1-24, wherein R^L is cyclobutyl.~~

826. The compound of any one of claims 1-236, wherein R^L is $NR^{11}R^{12}$.

279. The compound of any one of claims 1-246, wherein R^L is , wherein each C_1-C_6alkyl and C_3-C_6cycloalkyl may be optionally substituted by 1, 2, or 3 independent occurrences of fluorine; U is N or CR^{13}; V is selected from the group consisting of oxygen, $C(R^{34})_2$, and NR^6; r is 0, 1, or 2; q is 1, 2, or 3; R^{13} is selected from H and C_1-C_3alkyl; and each occurrence of R^{34} is independently selected from H, C_1-C_3alkyl, and C_3-C_5cycloalkyl, wherein C_1-C_3alkyl and C_3-C_5cycloalkyl may be optionally substituted by one or more independent occurrences of fluorine, or two R^{34} are joined together with the carbon to which they are attached to form a C_3-C_6cycloalkyl; provided that when r is 0 and q is 1, then U is not CR^{13} and V is not O, and when r or q is 1, then U is not N and V is not O or NR^6.

~~28. The compound of any one of claims 1-27, wherein n is 3.~~

2910. ~~A~~ The compound of claim 1 represented by:



Formula IB

or a pharmaceutically acceptable salt thereof, wherein:

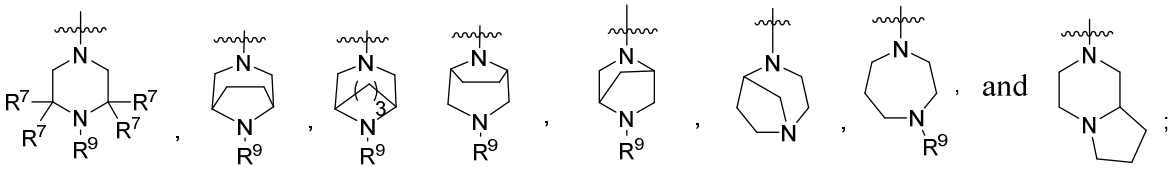
n is 2, 3, or 4;

R^1 is selected from the group consisting of halogen, cyano, C_1-C_5alkyl, and C_3-C_5cycloalkyl, wherein C_1-C_5alkyl and C_3-C_5cycloalkyl may be optionally substituted by one, two or three independent occurrences of fluorine;

R^2 is selected from the group consisting of C_1-C_2alkyl and C_3-C_4cycloalkyl, and halogen, wherein C_1-C_2alkyl and C_3-C_4cycloalkyl may be optionally substituted by one, two or three independent occurrences of fluorine;

R^3 is selected from the group consisting of H, C_1-C_3alkyl, and C_3-C_5cycloalkyl, wherein C_1-C_3alkyl and C_3-C_5cycloalkyl may be optionally substituted by one or more independent occurrences of fluorine;

R^4 is selected from the group consisting of:

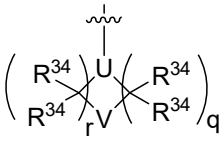


;

R^9 is selected from the group consisting of H, C_1-C_6alkyl, C_3-C_6cycloalkyl, $C(=O)R^5$, SO_2R^5, C-linked heterocyclyl having at least one nitrogen and optionally having an additional ring nitrogen or oxygen and heteroaryl, wherein C_1-C_6alkyl and C_3-C_6cycloalkyl may be optionally substituted by one or more independent occurrences of fluorine;

R^5 is selected from the group consisting of H, C_1-C_6alkyl, C_3-C_6cycloalkyl, and heterocyclyl, wherein C_1-C_6alkyl and C_3-C_6cycloalkyl may be optionally substituted by one or more independent occurrences of fluorine;

each occurrence of R^7 is independently selected from the group consisting of H, C_1-C_6 alkyl, and C_3-C_6cycloalkyl, wherein C_1-C_6alkyl and C_3-C_6cycloalkyl may be optionally substituted by one or more independent occurrences of fluorine, or two R^7 are joined together with the atom to which they are attached to form oxo;

R^L is selected from the group consisting of C_1-C_6alkyl and C_3-C_6cycloalkyl, $NR^{11}R^{12}$, and , wherein each C_1-C_6alkyl and C_3-C_6cycloalkyl may be optionally substituted by 1, 2, or 3 independent occurrences of fluorine;

U is N or CR^{13};

V is selected from the group consisting of oxygen, $C(R^{34})_2$, and NR^6;

r is 0, 1, or 2;

q is 1, 2, or 3;

R^6 is selected from the group consisting of H, C_1-C_6alkyl, C_3-C_6cycloalkyl, $C(=O)R^5$, SO_2R^5, C-linked heterocyclyl having at least one nitrogen and optionally having an additional ring nitrogen or oxygen and heteroaryl, wherein C_1-C_6alkyl and C_3-C_6cycloalkyl may be optionally substituted by one or more independent occurrences of fluorine;

R^{11} is selected from the group consisting of H, C_1-C_3alkyl, and C_3-C_5cycloalkyl, wherein C_1-C_3alkyl and C_3-C_5cycloalkyl may be optionally substituted by one or more independent occurrences of fluorine;

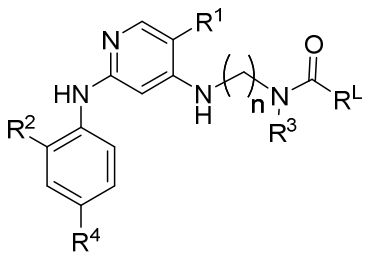
R^{12} is selected from the group consisting of H, C_1-C_3alkyl, and C_3-C_5cycloalkyl, wherein C_1-C_3alkyl and C_3-C_5cycloalkyl may be optionally substituted by one or more independent occurrences of fluorine;

R^{13} is selected from H and C_1-C_3alkyl; and

each occurrence of R^{34} is independently selected from H, C_1-C_3alkyl, and C_3-C_5cycloalkyl, wherein C_1-C_3alkyl and C_3-C_5cycloalkyl may be optionally substituted by one or more independent occurrences of fluorine, or two R^{34} are joined together with the carbon to which they are attached to form a C_3-C_6cycloalkyl;

provided that both of X and Y are not N, when r is 0 and q is 1, then U is not CR^{13} and V is not O, and when r or q is 1, then U is not N and V is not O or NR^6.

~~30~~11. ~~A~~ The compound of claim 1 represented by:



or a pharmaceutically acceptable salt thereof, wherein:

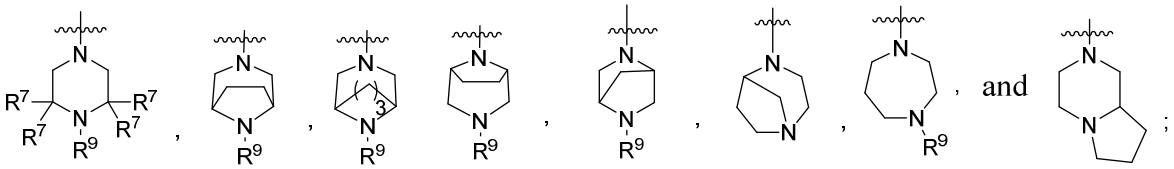
n is 2, 3, or 4;

R^1 is selected from the group consisting of halogen, cyano, C_1-C_5alkyl, and C_3-C_5cycloalkyl, wherein C_1-C_5alkyl and C_3-C_5cycloalkyl may be optionally substituted by one, two or three independent occurrences of fluorine;

R^2 is selected from the group consisting of C_1-C_2alkyl and C_3-C_4cycloalkyl, and halogen, wherein C_1-C_2alkyl and C_3-C_4cycloalkyl may be optionally substituted by one, two or three independent occurrences of fluorine;

R^3 is selected from the group consisting of H, C_1-C_3alkyl, and C_3-C_5cycloalkyl, wherein C_1-C_3alkyl and C_3-C_5cycloalkyl may be optionally substituted by one or more independent occurrences of fluorine;

R^4 is selected from the group consisting of:

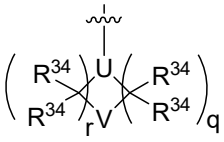


;

R^9 is independently selected from the group consisting of H, C_1-C_6alkyl, C_3-C_6cycloalkyl, C(=O)R^5, SO_2R^5, C-linked heterocyclyl having at least one nitrogen and optionally having an additional ring nitrogen or oxygen and heteroaryl, wherein C_1-C_6alkyl and C_3-C_6cycloalkyl may be optionally substituted by one or more independent occurrences of fluorine;

R^5 is selected from the group consisting of H, C_1-C_6alkyl, C_3-C_6cycloalkyl, and heterocyclyl, wherein C_1-C_6alkyl and C_3-C_6cycloalkyl may be optionally substituted by one or more independent occurrences of fluorine;

each occurrence of R^7 is independently selected from the group consisting of H, C_1-C_6 alkyl, and C_3-C_6cycloalkyl, wherein C_1-C_6alkyl and C_3-C_6cycloalkyl may be optionally substituted by one or more independent occurrences of fluorine, or two R^7 are joined together with the atom to which they are attached to form oxo;

R^L is selected from the group consisting of C_1-C_6alkyl and C_3-C_6cycloalkyl, $NR^{11}R^{12}$, and , wherein each C_1-C_6alkyl and C_3-C_6cycloalkyl may be optionally substituted by 1, 2, or 3 independent occurrences of fluorine;

U is N or CR^{13};

V is selected from the group consisting of oxygen, $C(R^{34})_2$, and NR^6;

r is 0, 1, or 2;

q is 1, 2, or 3;

R^6 is selected from the group consisting of H, C_1-C_6alkyl, C_3-C_6cycloalkyl, $C(=O)R^5$, SO_2R^5, C-linked heterocyclyl having at least one nitrogen and optionally having an additional ring nitrogen or oxygen and heteroaryl, wherein C_1-C_6alkyl and C_3-C_6cycloalkyl may be optionally substituted by one or more independent occurrences of fluorine;

R^{11} is selected from the group consisting of H, C_1-C_3alkyl, and C_3-C_5cycloalkyl, wherein C_1-C_3alkyl and C_3-C_5cycloalkyl may be optionally substituted by one or more independent occurrences of fluorine;

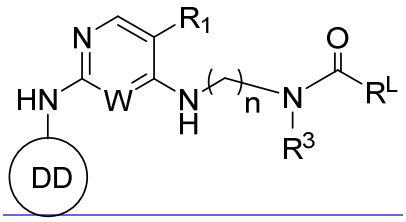
R^{12} is selected from the group consisting of H, C_1-C_3alkyl, and C_3-C_5cycloalkyl, wherein C_1-C_3alkyl and C_3-C_5cycloalkyl may be optionally substituted by one or more independent occurrences of fluorine;

R^{13} is selected from H and C_1-C_3alkyl; and

each occurrence of R^{34} is independently selected from H, C_1-C_3alkyl, and C_3-C_5cycloalkyl, wherein C_1-C_3alkyl and C_3-C_5cycloalkyl may be optionally substituted by one or more independent occurrences of fluorine, or two R^{34} are joined together with the carbon to which they are attached to form a C_3-C_6cycloalkyl;

provided that both of X and Y are not N, when r is 0 and q is 1, then U is not CR^{13} and V is not O, and when r or q is 1, then U is not N and V is not O or NR^6.

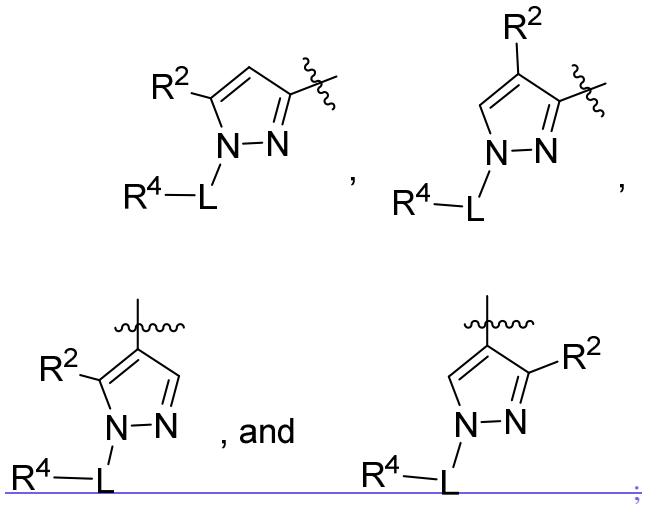
~~31. A compound represented by:~~



Formula ID

or a pharmaceutically acceptable salt, enantiomer, stereoisomer, or tautomer thereof, wherein:

ring DD is selected from the group consisting of



;

W is CH or N;

R^1 is selected from the group consisting of halogen, cyano, C_1-C_5alkyl, and C_3-C_5cycloalkyl, wherein C_1-C_5alkyl and C_3-C_5cycloalkyl may be optionally substituted by one, two or three independent occurrences of fluorine;

R^2 is selected from the group consisting of halogen, cyano, C_1-C_5alkyl, C_3-C_6cycloalkyl, C_2-C_5alkenyl, C_2-C_5alkynyl, C_1-C_5alkoxy, and C_1-C_5alkoxy-C_2-C_5alkyl, wherein each C_1-C_5alkyl, C_3-C_6cycloalkyl, C_2-C_5alkenyl, C_2-C_5alkynyl, and C_1-C_5alkoxy may be optionally substituted by one, two, or three independent occurrences of fluorine or cyano;

R^3 is selected from the group consisting of H, C_1-C_3alkyl, and C_3-C_5cycloalkyl, wherein C_1-C_3alkyl and C_3-C_5cycloalkyl may be optionally substituted by one or more independent occurrences of fluorine;

R^4 is selected from the group consisting of B, D, NR^6R^9, NR^6-$(C(R^{10})_2)_p$-NR^6R^9, C(O)-NR^6R^9; C(O)-B; C(O)-D , and CN;

B is selected from an N-linked heterocyclyl having at least one nitrogen and optionally having an additional ring nitrogen or oxygen and heteroaryl, wherein B may be optionally substituted on one or more available carbons by R^7 and may be optionally substituted on an available nitrogen by R^9;

D is selected from a C-linked heterocyclyl having at least one nitrogen and optionally having an additional ring nitrogen or oxygen and heteroaryl, wherein D may be optionally

substituted on one or more available carbons by R^7 and may be optionally substituted on an available nitrogen by R^9;

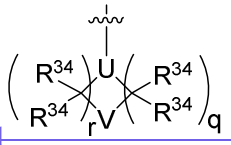
each occurrence of R^7 is independently selected from the group consisting of H, C_1-C_6alkyl, C_3-C_6cycloalkyl, cyano, and $(C(R^{10})_2)_h$-NR^6R^9, wherein C_1-C_6alkyl and C_3-C_6cycloalkyl may be optionally substituted by one or more independent occurrences of fluorine, or two R^7 are joined together with the atom to which they are attached to form oxo;

R^6 is selected from the group consisting of H, C_1-C_6alkyl, C_3-C_6cycloalkyl, C_1-C_5alkoxy-C_2-C_5alkyl, $C(=O)R^5$, SO_2R^5, C-linked heterocyclyl having at least one nitrogen and optionally having an additional ring nitrogen or oxygen, and heteroaryl, wherein C_1-C_6alkyl and C_3-C_6cycloalkyl may be optionally substituted by one or more independent occurrences of fluorine;

R^9 is selected from the group consisting of H, C_1-C_6alkyl, C_3-C_6cycloalkyl, C_1-C_5alkoxy-C_2-C_5alkyl, $C(=O)R^5$, SO_2R^5, C-linked heterocyclyl having at least one nitrogen and optionally having an additional ring nitrogen or oxygen, and heteroaryl, wherein C_1-C_6alkyl and C_3-C_6cycloalkyl may be optionally substituted by one or more independent occurrences of fluorine;

R^5 is selected from the group consisting of H, C_1-C_6alkyl, C_3-C_6cycloalkyl, and heterocyclyl, wherein C_1-C_6alkyl and C_3-C_6cycloalkyl may be optionally substituted by one or more independent occurrences of fluorine;

each occurrence of R^{10} is independently selected from the group consisting of H, C_1-C_3alkyl, and C_3-C_5cycloalkyl, wherein C_1-C_3alkyl and C_3-C_5cycloalkyl may be optionally substituted by one or more independent occurrences of fluorine, or two R^{10} are joined together with the carbon to which they are attached to form a C_3-C_5cycloalkyl;

R^L is selected from the group consisting of C_1-C_6alkyl and C_3-C_6cycloalkyl, $NR^{11}R^{12}$, and , wherein each C_1-C_6alkyl and C_3-C_6cycloalkyl may be optionally substituted by 1, 2, or 3 independent occurrences of fluorine;

U is N or CR^{13};

V is selected from the group consisting of oxygen, $C(R^{34})_2$, and NR^6;

r is 0, 1, or 2,

q is 1, 2, or 3;

R^{11} is selected from the group consisting of H, C_1-C_3alkyl, and C_3-C_5cycloalkyl, wherein C_1-C_3alkyl and C_3-C_5cycloalkyl may be optionally substituted by one or more independent occurrences of fluorine;

R^{12} is selected from the group consisting of H, C_1-C_3alkyl, and C_3-C_5cycloalkyl, wherein C_1-C_3alkyl and C_3-C_5cycloalkyl may be optionally substituted by one or more independent occurrences of fluorine;

R^{13} is selected from H and C_1-C_3alkyl;

each occurrence of R^{34} is independently selected from H, C_1-C_3alkyl, and C_3-C_5cycloalkyl, wherein C_1-C_3alkyl and C_3-C_5cycloalkyl may be optionally substituted by one or more independent occurrences of fluorine, or two R^{34} are joined together with the carbon to which they are attached to form a C_3-C_6cycloalkyl;

L is $-(C(R^{10})_2)_m-$;

h is 1, 2, or 3;

m is 0, 1, 2, or 3;

n is 2, 3, or 4; and

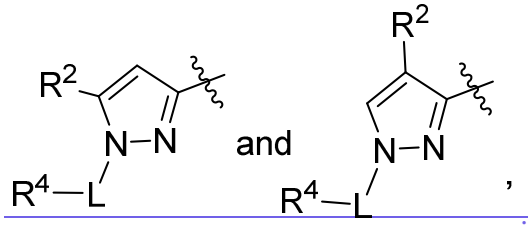
p is 2 or 3;

provided that when m is 0, R^4 is C-linked to the pyrazolyl ring, when m is 1, R^4 is C-linked to L, and when m is 2 or 3, R^4 is N-linked or C-linked to L; and further provided that when r is 0 and q is 1, then U is not CR^{13} and V is not O, and when r or q is 1, then U is not N and V is not O or NR^6.

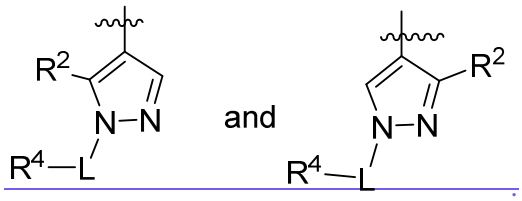
32. The compound of claim 31, wherein W is N.

33. The compound of claim 31, wherein W is CH.

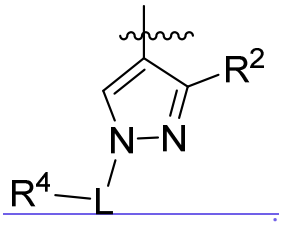
34. The compound of any one of claims 31-33, wherein ring DD is selected from the group consisting of:



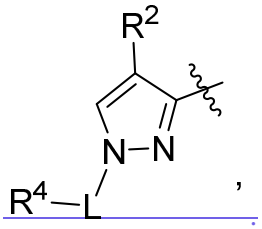
35. The compound of any one of claims 31-33, wherein ring DD is selected from the group consisting of:



36. The compound of any one of claims 31-33, wherein ring DD is:

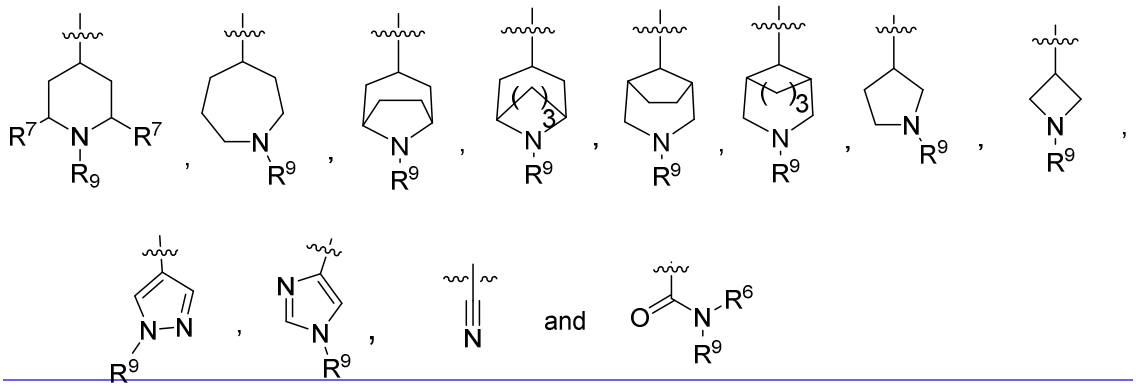


37. The compound of any one of claims 31-33, wherein ring DD is:



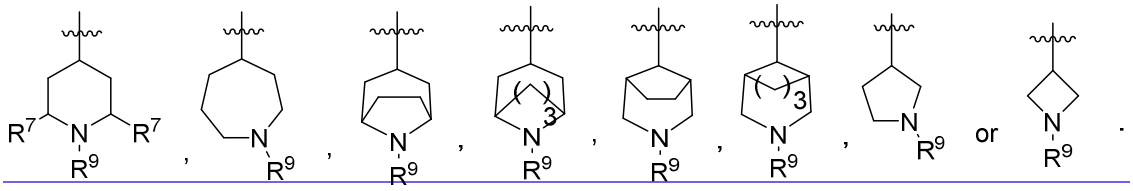
38. The compound of any one of claims 31-37, wherein R^4 is D.

39. The compound of any one of claims 31-38, wherein R^4 is selected from the group consisting of:



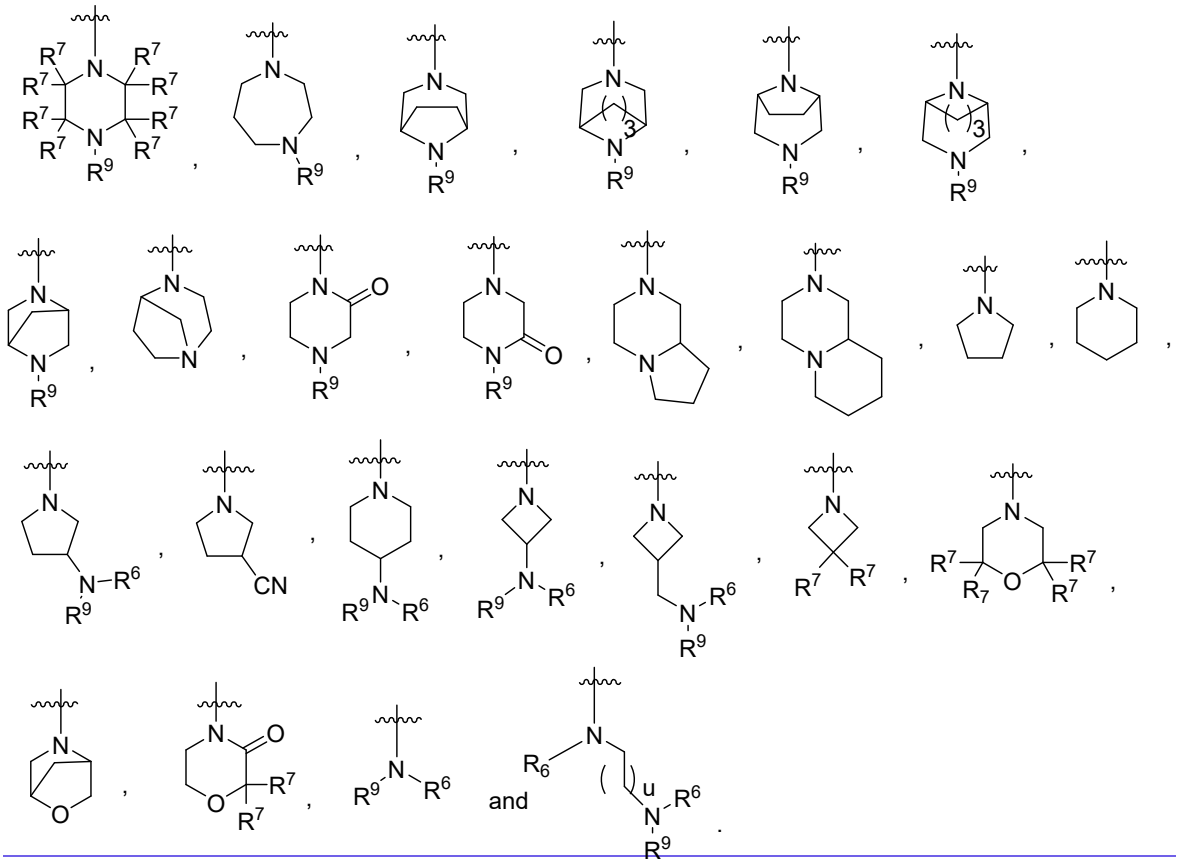
.

40. The compound of any one of claims 31-39, wherein R^4 is selected from the group consisting of:



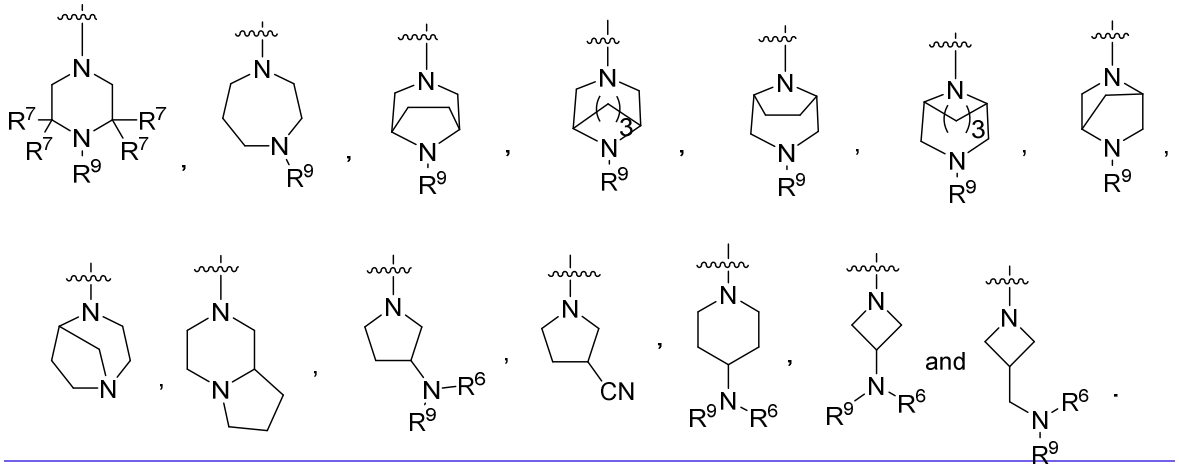
41. The compound of any one of claims 31-37, wherein R^4 is B.

42. The compound of any one of claims 31-37 or claim 41, wherein R^4 is selected from the group consisting of:

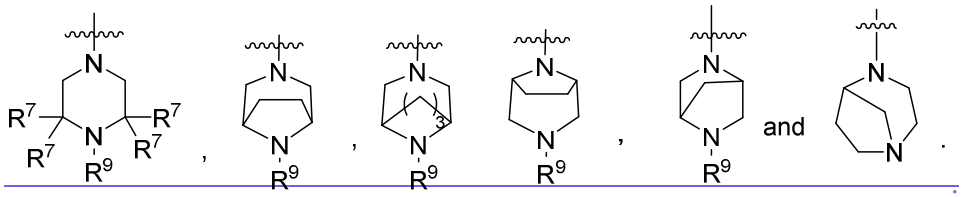


~~wherein u is 1 or 2.~~

~~43. The compound of any one of claims 31-37 or claim 41, wherein R^4 is selected from the group consisting of:~~



~~44. The compound of any one of claims 31-37 or claim 41, wherein R^4 is selected from the group consisting of:~~



45. The compound of any one of claims 31-33, wherein L is $-(CH_2)_m-$.

46. The compound of any one of claims 31-45, wherein m is 0.

47. The compound of any one of claims 31-45, wherein m is 2.

48. The compound of any one of claims 31-45, wherein m is 3.

49. The compound of any one of claims 31-48, wherein R^1 is selected from the group consisting of halogen, C_1-C_5alkyl, and C_3-C_5cycloalkyl, wherein C_1-C_5alkyl and C_3-C_5cycloalkyl may be optionally substituted with one, two, or three independent occurrences of fluorine.

50. The compound of any one of claims 31-49, wherein R^1 is CF_3.

51. The compound of any one of claims 31-49, wherein R^1 is CF_2H.

52. The compound of any one of claims 31-49, wherein R^1 is selected from the group consisting of chloro, bromo, and fluoro.

53. The compound of claim 52, wherein R^1 is bromo.

54. The compound of any one of claims 31-49, wherein R^1 is cyclopropyl.

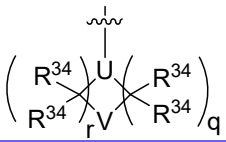
55. The compound of any one of claims 31-54, wherein R^2 is selected from the group consisting of C_3-C_5cycloalkyl, C_1-C_5alkyl, halogen, cyano, C_2-C_5alkenyl, and C_2-C_5alknyl, wherein C_3-C_5cycloalkyl, C_1-C_5alkyl, C_2-C_5alkenyl, and C_2-C_5alknyl may be optionally substituted with one, two, or three independent occurrences of fluorine.

~~56. The compound of any one of claims 31-55, wherein R^2 is selected from the group consisting of C_{1-2}alkyl and C_{3-4}cycloalkyl.~~

~~57. The compound of any one of claims 31-56, wherein R^3 is selected from the group consisting of H, C_1-C_3alkyl, and C_3-C_5cycloalkyl wherein C_1-C_3alkyl and C_3-C_5cycloalkyl may be optionally substituted by one or more independent occurrences of fluorine.~~

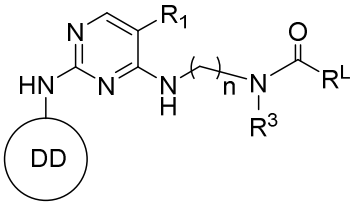
~~58. The compound of any one of claims 31-57, wherein R^L is cyclobutyl.~~

~~59. The compound of any one of claims 31-58, wherein R^L is $NR^{11}R^{12}$.~~

~~60. The compound of any one of claims 31-59, wherein R^L is~~  ~~, wherein each C_1-C_6alkyl and C_3-C_6cycloalkyl may be optionally substituted by 1, 2, or 3 independent occurrences of fluorine; U is N or CR^{13}; V is selected from the group consisting of oxygen, $C(R^{34})_2$, and NR^6; r is 0, 1, or 2; q is 1, 2, or 3; R^{13} is selected from H and C_1-C_3alkyl; and each occurrence of R^{34} is independently selected from H, C_1-C_3alkyl, and C_3-C_5cycloalkyl, wherein C_1-C_3alkyl and C_3-C_5cycloalkyl may be optionally substituted by one or more independent occurrences of fluorine, or two R^{34} are joined together with the carbon to which they are attached to form a C_3-C_6cycloalkyl; provided that when r is 0 and q is 1, then U is not CR^{13} and V is not O, and when r or q is 1, then U is not N and V is not O or NR^6.~~

~~61. The compound of any one of claims 31-60, wherein n is 3.~~

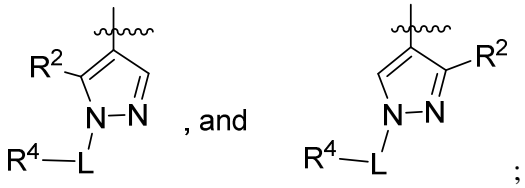
12~~62~~. A compound represented by:



Formula IE

or a pharmaceutically acceptable salt thereof, wherein:

ring DD is selected from the group consisting of:



;

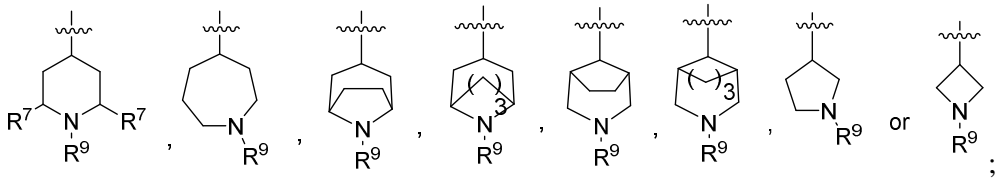
n is 2, 3, or 4;

R^1 is selected from the group consisting of halogen, cyano, C_1-C_5alkyl, and C_3-C_5cycloalkyl, wherein C_1-C_5alkyl and C_3-C_5cycloalkyl may be optionally substituted by one, two or three independent occurrences of fluorine;

R^2 is selected from the group consisting of C_1-C_2alkyl and C_3-C_4cycloalkyl, and halogen, wherein C_1-C_2alkyl and C_3-C_4cycloalkyl may be optionally substituted by one, two or three independent occurrences of fluorine;

R^3 is selected from the group consisting of H, C_1-C_3alkyl, and C_3-C_5cycloalkyl, wherein C_1-C_3alkyl and C_3-C_5cycloalkyl may be optionally substituted by one or more independent occurrences of fluorine;

R^4 is selected from the group consisting of:

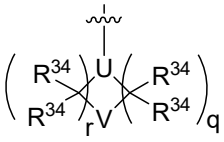


;

R^9 is selected from the group consisting of H, C_1-C_6alkyl, C_3-C_6cycloalkyl, $C(=O)R^5$, SO_2R^5, C-linked heterocyclyl having at least one nitrogen and optionally having an additional ring nitrogen or oxygen and heteroaryl, wherein C_1-C_6alkyl and C_3-C_6cycloalkyl may be optionally substituted by one or more independent occurrences of fluorine;

R^5 is selected from the group consisting of H, C_1-C_6alkyl, C_3-C_6cycloalkyl, and heterocyclyl, wherein C_1-C_6alkyl and C_3-C_6cycloalkyl may be optionally substituted by one or more independent occurrences of fluorine;

each occurrence of R^7 is independently selected from the group consisting of H, C_1-C_6 alkyl, and C_3-C_6cycloalkyl, wherein C_1-C_6alkyl and C_3-C_6cycloalkyl may be optionally substituted by one or more independent occurrences of fluorine, or two R^7 are joined together with the atom to which they are attached to form oxo;

R^L is selected from the group consisting of C_1-C_6alkyl and C_3-C_6cycloalkyl, $NR^{11}R^{12}$, and , wherein each C_1-C_6alkyl and C_3-C_6cycloalkyl may be optionally substituted by 1, 2, or 3 independent occurrences of fluorine;

U is N or CR^{13};

V is selected from the group consisting of oxygen, $C(R^{34})_2$, and NR^6;

r is 0, 1, or 2;

q is 1, 2, or 3;

R^6 is selected from the group consisting of H, C_1-C_6alkyl, C_3-C_6cycloalkyl, $C(=O)R^5$, SO_2R^5, C-linked heterocyclyl having at least one nitrogen and optionally having an additional ring nitrogen or oxygen and heteroaryl, wherein C_1-C_6alkyl and C_3-C_6cycloalkyl may be optionally substituted by one or more independent occurrences of fluorine;

R^{11} is selected from the group consisting of H, C_1-C_3alkyl, and C_3-C_5cycloalkyl, wherein C_1-C_3alkyl and C_3-C_5cycloalkyl may be optionally substituted by one or more independent occurrences of fluorine;

R^{12} is selected from the group consisting of H, C_1-C_3alkyl, and C_3-C_5cycloalkyl, wherein C_1-C_3alkyl and C_3-C_5cycloalkyl may be optionally substituted by one or more independent occurrences of fluorine;

R^{13} is selected from H and C_1-C_3alkyl;

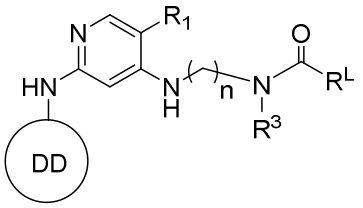
each occurrence of R^{34} is independently selected from H, C_1-C_3alkyl, and C_3-C_5cycloalkyl, wherein C_1-C_3alkyl and C_3-C_5cycloalkyl may be optionally substituted by one or more independent occurrences of fluorine, or two R^{34} are joined together with the carbon to which they are attached to form a C_3-C_6cycloalkyl; and

L is $-(C(R^{10})_2)_m-$;

m is 0, 1, 2, or 3;

provided that when m is 0, R_4 is C-linked to the pyrazolyl ring, when m is 1, R^4 is C-linked to L, and when m is 2 or 3, R^4 is N-linked or C-linked to L; and further provided that when r is 0 and q is 1, then U is not CR^{13} and V is not O, and when r or q is 1, then U is not N and V is not O or NR^6.

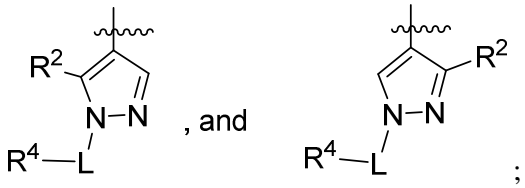
~~63~~13. A compound represented by:



Formula IF

or a pharmaceutically acceptable salt thereof, wherein:

ring DD is selected from the group consisting of:



;

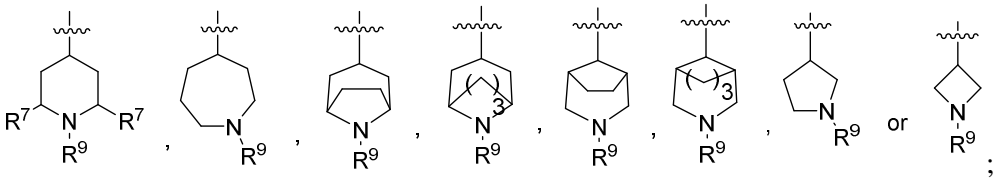
n is 2, 3, or 4;

R^1 is selected from the group consisting of halogen, cyano, C_1-C_5alkyl, and C_3-C_5cycloalkyl, wherein C_1-C_5alkyl and C_3-C_5cycloalkyl may be optionally substituted by one, two or three independent occurrences of fluorine;

R^2 is selected from the group consisting of C_1-C_2alkyl and C_3-C_4cycloalkyl, and halogen, wherein C_1-C_2alkyl and C_3-C_4cycloalkyl may be optionally substituted by one, two or three independent occurrences of fluorine;

R^3 is selected from the group consisting of H, C_1-C_3alkyl, and C_3-C_5cycloalkyl, wherein C_1-C_3alkyl and C_3-C_5cycloalkyl may be optionally substituted by one or more independent occurrences of fluorine;

R^4 is selected from the group consisting of:

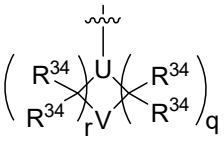


;

R^9 is selected from the group consisting of H, C_1-C_6alkyl, C_3-C_6cycloalkyl, $C(=O)R^5$, SO_2R^5, C-linked heterocyclyl having at least one nitrogen and optionally having an additional ring nitrogen or oxygen and heteroaryl, wherein C_1-C_6alkyl and C_3-C_6cycloalkyl may be optionally substituted by one or more independent occurrences of fluorine;

R^5 is selected from the group consisting of H, C_1-C_6alkyl, C_3-C_6cycloalkyl, and heterocyclyl, wherein C_1-C_6alkyl and C_3-C_6cycloalkyl may be optionally substituted by one or more independent occurrences of fluorine;

each occurrence of R^7 is independently selected from the group consisting of H, C_1-C_6 alkyl, and C_3-C_6cycloalkyl, wherein C_1-C_6alkyl and C_3-C_6cycloalkyl may be optionally substituted by one or more independent occurrences of fluorine, or two R^7 are joined together with the atom to which they are attached to form oxo;

R^L is selected from the group consisting of C_1-C_6alkyl and C_3-C_6cycloalkyl, $NR^{11}R^{12}$, and , wherein each C_1-C_6alkyl and C_3-C_6cycloalkyl may be optionally substituted by 1, 2, or 3 independent occurrences of fluorine;

U is N or CR^{13};

V is selected from the group consisting of oxygen, $C(R^{34})_2$, and NR^6;

r is 0, 1, or 2;

q is 1, 2, or 3;

R^6 is selected from the group consisting of H, C_1-C_6alkyl, C_3-C_6cycloalkyl, $C(=O)R^5$, SO_2R^5, C-linked heterocyclyl having at least one nitrogen and optionally having an additional ring nitrogen or oxygen and heteroaryl, wherein C_1-C_6alkyl and C_3-C_6cycloalkyl may be optionally substituted by one or more independent occurrences of fluorine;

R^{11} is selected from the group consisting of H, C_1-C_3alkyl, and C_3-C_5cycloalkyl, wherein C_1-C_3alkyl and C_3-C_5cycloalkyl may be optionally substituted by one or more independent occurrences of fluorine;

R^{12} is selected from the group consisting of H, C_1-C_3alkyl, and C_3-C_5cycloalkyl, wherein C_1-C_3alkyl and C_3-C_5cycloalkyl may be optionally substituted by one or more independent occurrences of fluorine;

R^{13} is selected from H and C_1-C_3alkyl;

each occurrence of R^{34} is independently selected from H, C_1-C_3alkyl, and C_3-C_5cycloalkyl, wherein C_1-C_3alkyl and C_3-C_5cycloalkyl may be optionally substituted by one or more independent occurrences of fluorine, or two R^{34} are joined together with the carbon to which they are attached to form a C_3-C_6cycloalkyl; and

L is $-(C(R^{10})_2)_m-$;

m is 0, 1, 2, or 3;

provided that when m is 0, R_4 is C-linked to the pyrazolyl ring, when m is 1, R^4 is C-linked to L, and when m is 2 or 3, R^4 is N-linked or C-linked

to L; and further provided that when r is 0 and q is 1, then U is not CR^{13} and V is not O, and when r or q is 1, then U is not N and V is not O or NR^6.

~~64~~14. The~~A~~ compound of claim 1 selected from the group consisting of: N-(3-((5-cyclopropyl-2-((3-methyl-1-(piperidin-4-yl)-1H-pyrazol-4-yl)amino)pyrimidin-4-yl)amino)propyl)cyclobutanecarboxamide, N-(3-((5-cyclopropyl-2-((2-methoxy-4-(4-methylpiperazin-1-yl)phenyl)amino)pyrimidin-4-yl)amino)propyl)cyclobutanecarboxamide, N-(3-((5-cyclopropyl-2-((3-methyl-1-(1-methylpiperidin-4-yl)-1H-pyrazol-4-yl)amino)pyrimidin-4-yl)amino)propyl)cyclobutanecarboxamide, N-(3-((2-((2-methyl-4-(4-methylpiperazin-1-yl)phenyl)amino)-5-(trifluoromethyl)pyrimidin-4-yl)amino)propyl)pivalamide, N-(3-((5-bromo-2-((2-isopropyl-4-(4-methylpiperazin-1-yl)phenyl)amino)pyrimidin-4-yl)amino)propyl)cyclobutanecarboxamide, N-(3-((5-cyclopropyl-2-((2-isopropyl-4-(4-methylpiperazin-1-yl)phenyl)amino)pyrimidin-4-yl)amino)propyl)cyclobutanecarboxamide, N-(3-((2-((2-cyclopropyl-4-(4-methylpiperazin-1-yl)phenyl)amino)-5-(trifluoromethyl)pyrimidin-4-yl)amino)propyl)cyclobutanecarboxamide, N-(3-((2-((1-(1-amino-2-methyl-1-oxopropan-2-yl)-3-methyl-1H-pyrazol-4-yl)amino)-5-(trifluoromethyl)pyrimidin-4-yl)amino)propyl)cyclobutanecarboxamide, N-(3-((2-((2-methoxy-4-(4-methylpiperazin-1-yl)phenyl)amino)-5-(trifluoromethyl)pyrimidin-4-yl)amino)propyl)cyclobutanecarboxamide, N-(3-((2-((1-(2-cyanopropan-2-yl)-3-methyl-1H-pyrazol-4-yl)amino)-5-(trifluoromethyl)pyrimidin-4-yl)amino)propyl)cyclobutanecarboxamide, N-(3-((2-((4-methyl-6-(4-methylpiperazin-1-yl)pyridin-3-yl)amino)-5-(trifluoromethyl)pyridin-4-yl)amino)propyl)cyclobutanecarboxamide, N-(3-((5-chloro-2-((2-isopropoxy-4-(4-methylpiperazin-1-yl)phenyl)amino)pyrimidin-4-yl)amino)propyl)cyclobutanecarboxamide, N-(3-((5-bromo-2-((2-ethyl-4-(4-methylpiperazin-1-yl)phenyl)amino)pyrimidin-4-yl)amino)propyl)cyclobutanecarboxamide, N-(3-((5-chloro-2-((3-methyl-1-(1-methylpiperidin-4-yl)-1H-pyrazol-4-yl)amino)pyrimidin-4-yl)amino)propyl)-N-methylcyclobutanecarboxamide, N-(3-((5-chloro-2-((2-methyl-4-(piperidin-4-yl)phenyl)amino)pyrimidin-4-yl)amino)propyl)-N-methylcyclobutanecarboxamide, N-methyl-N-(3-((2-((2-methyl-4-(piperidin-4-yl)phenyl)amino)-5-(trifluoromethyl)pyrimidin-4-yl)amino)propyl)cyclobutanecarboxamide, N-(3-((5-chloro-2-((2-methyl-4-(1-methylpiperidin-4-yl)phenyl)amino)pyrimidin-4-yl)amino)propyl)-N-methylcyclobutanecarboxamide, N-methyl-N-(3-((2-((2-methyl-4-(1-methylpiperidin-4-

yl)phenyl)amino)-5-(trifluoromethyl)pyrimidin-4-yl)amino)propyl)cyclobutanecarboxamide, N-(3-((2-((1-(1-cyclopropylpiperidin-4-yl)-3-methyl-1H-pyrazol-4-yl)amino)-5-(trifluoromethyl)pyrimidin-4-yl)amino)propyl)-N-methylcyclobutanecarboxamide, N-(3-((2-((3-methyl-1-(piperidin-4-yl)-1H-pyrazol-4-yl)amino)-5-(trifluoromethyl)pyrimidin-4-yl)amino)propyl)cyclobutanecarboxamide, N-(3-((2-((1-(1-isopropylpiperidin-4-yl)-3-methyl-1H-pyrazol-4-yl)amino)-5-(trifluoromethyl)pyrimidin-4-yl)amino)propyl)cyclobutanecarboxamide, N-(3-((2-((1-(1-isobutylpiperidin-4-yl)-3-methyl-1H-pyrazol-4-yl)amino)-5-(trifluoromethyl)pyrimidin-4-yl)amino)propyl)cyclobutanecarboxamide, N-(3-((5-bromo-2-((3-methyl-1-(1-d3-methylpiperidin-4-yl)-1H-pyrazol-4-yl)amino)pyrimidin-4-yl)amino)propyl)cyclobutanecarboxamide, N-(3-((2-((3-methyl-1-(1-d3-methylpiperidin-4-yl)-1H-pyrazol-4-yl)amino)-5-(trifluoromethyl)pyrimidin-4-yl)amino)propyl)cyclobutanecarboxamide, N-(3-((2-((2-methyl-4-(4-methylpiperazin-1-yl)phenyl)amino)-5-(trifluoromethyl)pyrimidin-4-yl)amino)propyl)cyclobutanecarboxamide, N-(3-((2-((2-ethyl-4-(4-methylpiperazin-1-yl)phenyl)amino)-5-(trifluoromethyl)pyrimidin-4-yl)amino)propyl)cyclobutanecarboxamide, N-(3-((2-((4-methyl-6-(4-methylpiperazin-1-yl)pyridin-3-yl)amino)-5-(trifluoromethyl)pyrimidin-4-yl)amino)propyl)cyclobutanecarboxamide, N-(3-((2-((4-methyl-6-morpholinopyridin-3-yl)amino)-5-(trifluoromethyl)pyrimidin-4-yl)amino)propyl)cyclobutanecarboxamide, N-(3-((2-((2-isopropyl-4-(4-methylpiperazin-1-yl)phenyl)amino)-5-(trifluoromethyl)pyrimidin-4-yl)amino)propyl)cyclobutanecarboxamide, N-(3-((5-cyclopropyl-2-((2-ethyl-4-(4-methylpiperazin-1-yl)phenyl)amino)pyrimidin-4-yl)amino)propyl)cyclobutanecarboxamide, N-(3-((5-bromo-2-((2-cyclopropyl-4-(4-methylpiperazin-1-yl)phenyl)amino)pyrimidin-4-yl)amino)propyl)cyclobutanecarboxamide, N-(3-((2-((2-ethyl-4-((1R,5S)-8-methyl-3,8-diazabicyclo[3.2.1]octan-3-yl)phenyl)amino)-5-(trifluoromethyl)pyrimidin-4-yl)amino)propyl)cyclobutanecarboxamide, N-(3-((2-((2-ethyl-4-(5-methyl-2,5-diazabicyclo[2.2.1]heptan-2-yl)phenyl)amino)-5-(trifluoromethyl)pyrimidin-4-yl)amino)propyl)cyclobutanecarboxamide, N-(3-((2-((4-(1,4-diazabicyclo[3.2.1]octan-4-yl)-2-ethylphenyl)amino)-5-(trifluoromethyl)pyrimidin-4-yl)amino)propyl)cyclobutanecarboxamide, N-(3-((2-((2-ethyl-4-(hexahydropyrrolo[1,2-a]pyrazin-2(1H)-yl)phenyl)amino)-5-(trifluoromethyl)pyrimidin-4-yl)amino)propyl)cyclobutanecarboxamide, N-(3-((5-(difluoromethyl)-2-((2-ethyl-4-(4-methylpiperazin-1-yl)phenyl)amino)pyrimidin-4-yl)amino)propyl)cyclobutanecarboxamide, N-(3-((2-((2-ethyl-4-(4-methylpiperazin-1-yl)phenyl)amino)-5-(trifluoromethyl)pyrimidin-4-

yl)amino)propyl)-3,3-difluorocyclobutane-1-carboxamide, N-(3-((2-((2-ethyl-4-(4-methylpiperazin-1-yl)phenyl)amino)-5-(trifluoromethyl)pyrimidin-4-yl)amino)propyl)isobutyramide, N-(3-((2-((2-ethyl-4-(4-methylpiperazin-1-yl)phenyl)amino)-5-(trifluoromethyl)pyrimidin-4-yl)amino)propyl)pivalamide, N-(3-((2-((2-ethyl-4-(4-methylpiperazin-1-yl)phenyl)amino)-5-(trifluoromethyl)pyrimidin-4-yl)amino)propyl)cyclopropanecarboxamide, N-(3-((2-((2-ethyl-4-(4-methylpiperazin-1-yl)phenyl)amino)-5-(trifluoromethyl)pyrimidin-4-yl)amino)propyl)oxetane-3-carboxamide, N-(3-((2-((2-ethyl-4-(4-methylpiperazin-1-yl)phenyl)amino)-5-(trifluoromethyl)pyrimidin-4-yl)amino)propyl)tetrahydrofuran-3-carboxamide, N-(3-((2-((2-ethyl-4-(4-methylpiperazin-1-yl)phenyl)amino)-5-(trifluoromethyl)pyrimidin-4-yl)amino)propyl)tetrahydro-2H-pyran-4-carboxamide, N-(3-((5-bromo-2-((2-ethyl-4-(4-methylpiperazin-1-yl)phenyl)amino)pyrimidin-4-yl)amino)propyl)cyclobutanecarboxamide, N-(3-((5-bromo-2-((2-ethyl-4-(4-methylpiperazin-1-yl)phenyl)amino)pyrimidin-4-yl)amino)propyl)oxetane-3-carboxamide, N-(3-((5-bromo-2-((2-ethyl-4-(4-methylpiperazin-1-yl)phenyl)amino)pyrimidin-4-yl)amino)propyl)tetrahydrofuran-3-carboxamide, N-(3-((5-bromo-2-((2-ethyl-4-(4-methylpiperazin-1-yl)phenyl)amino)pyrimidin-4-yl)amino)propyl)tetrahydro-2H-pyran-4-carboxamide, N-(3-((2-((2-ethyl-4-(4-methylpiperazin-1-yl)phenyl)amino)-5-(trifluoromethyl)pyrimidin-4-yl)amino)propyl)-N-methylcyclobutanecarboxamide, N-(3-((2-((2-ethyl-4-((1R,5S)-8-methyl-3,8-diazabicyclo[3.2.1]octan-3-yl)phenyl)amino)-5-(trifluoromethyl)pyrimidin-4-yl)amino)propyl)-N-methylcyclobutanecarboxamide, N-(3-((2-((2-ethyl-4-(5-methyl-2,5-diazabicyclo[2.2.1]heptan-2-yl)phenyl)amino)-5-(trifluoromethyl)pyrimidin-4-yl)amino)propyl)-N-methylcyclobutanecarboxamide, N-(3-((2-((4-(1,4-diazabicyclo[3.2.1]octan-4-yl)-2-ethylphenyl)amino)-5-(trifluoromethyl)pyrimidin-4-yl)amino)propyl)-N-methylcyclobutanecarboxamide, N-(3-((2-((2-ethyl-4-(hexahydropyrrolo[1,2-a]pyrazin-2(1H)-yl)phenyl)amino)-5-(trifluoromethyl)pyrimidin-4-yl)amino)propyl)-N-methylcyclobutanecarboxamide, N-(3-((5-(difluoromethyl)-2-((2-ethyl-4-(4-methylpiperazin-1-yl)phenyl)amino)pyrimidin-4-yl)amino)propyl)-N-methylcyclobutanecarboxamide, N-(3-((2-((2-ethyl-4-(4-methylpiperazin-1-yl)phenyl)amino)-5-(trifluoromethyl)pyrimidin-4-yl)amino)propyl)-3,3-difluoro-N-methylcyclobutane-1-carboxamide, N-(3-((2-((2-ethyl-4-(4-methylpiperazin-1-yl)phenyl)amino)-5-(trifluoromethyl)pyrimidin-4-yl)amino)propyl)-N-methylisobutyramide, N-(3-((2-((2-ethyl-4-(4-methylpiperazin-1-yl)phenyl)amino)-5-(trifluoromethyl)pyrimidin-4-yl)amino)propyl)-N-methylpivalamide, N-(3-((2-((2-ethyl-4-(4-methylpiperazin-1-

yl)phenyl)amino)-5-(trifluoromethyl)pyrimidin-4-yl)amino)propyl)-N-methyloxetane-3-carboxamide, N-(3-((2-((2-ethyl-4-(4-methylpiperazin-1-yl)phenyl)amino)-5-(trifluoromethyl)pyrimidin-4-yl)amino)propyl)-N-methyltetrahydrofuran-3-carboxamide, N-(3-((2-((2-ethyl-4-(4-methylpiperazin-1-yl)phenyl)amino)-5-(trifluoromethyl)pyrimidin-4-yl)amino)propyl)-N-methyltetrahydro-2H-pyran-4-carboxamide, N-(3-((5-bromo-2-((2-ethyl-4-(4-methylpiperazin-1-yl)phenyl)amino)pyrimidin-4-yl)amino)propyl)-N-methylcyclobutanecarboxamide, N-(3-((5-bromo-2-((2-ethyl-4-(4-methylpiperazin-1-yl)phenyl)amino)pyrimidin-4-yl)amino)propyl)-N-methyloxetane-3-carboxamide, N-(3-((5-bromo-2-((2-ethyl-4-(4-methylpiperazin-1-yl)phenyl)amino)pyrimidin-4-yl)amino)propyl)-N-methyltetrahydrofuran-3-carboxamide, N-(3-((5-bromo-2-((2-ethyl-4-(4-methylpiperazin-1-yl)phenyl)amino)pyrimidin-4-yl)amino)propyl)-N-methyltetrahydro-2H-pyran-4-carboxamide, N-(3-((2-((2-ethyl-4-(4-methylpiperazin-1-yl)phenyl)amino)-5-(trifluoromethyl)pyrimidin-4-yl)amino)propyl)-1-methylazetidine-3-carboxamide, N-(3-((2-((2-ethyl-4-((1R,5S)-8-methyl-3,8-diazabicyclo[3.2.1]octan-3-yl)phenyl)amino)-5-(trifluoromethyl)pyrimidin-4-yl)amino)propyl)-1-methylazetidine-3-carboxamide, N-(3-((2-((2-ethyl-4-(5-methyl-2,5-diazabicyclo[2.2.1]heptan-2-yl)phenyl)amino)-5-(trifluoromethyl)pyrimidin-4-yl)amino)propyl)-1-methylazetidine-3-carboxamide, N-(3-((2-((4-(1,4-diazabicyclo[3.2.1]octan-4-yl)-2-ethylphenyl)amino)-5-(trifluoromethyl)pyrimidin-4-yl)amino)propyl)-1-methylazetidine-3-carboxamide, N-(3-((2-((2-ethyl-4-(hexahydropyrrolo[1,2-a]pyrazin-2(1H)-yl)phenyl)amino)-5-(trifluoromethyl)pyrimidin-4-yl)amino)propyl)-1-methylazetidine-3-carboxamide, N-(3-((2-((2-ethyl-4-(4-methylpiperazin-1-yl)phenyl)amino)-5-(trifluoromethyl)pyrimidin-4-yl)amino)propyl)-N,1-dimethylazetidine-3-carboxamide, N-(3-((5-chloro-2-((2-ethyl-4-(4-methylpiperazin-1-yl)phenyl)amino)pyrimidin-4-yl)amino)propyl)-1-methylazetidine-3-carboxamide, N-(3-((5-chloro-2-((2-ethyl-4-(4-methylpiperazin-1-yl)phenyl)amino)pyrimidin-4-yl)amino)propyl)-N,1-dimethylazetidine-3-carboxamide, N-(3-((5-bromo-2-((2-ethyl-4-(4-methylpiperazin-1-yl)phenyl)amino)pyrimidin-4-yl)amino)propyl)-1-methylazetidine-3-carboxamide, N-(3-((5-bromo-2-((2-ethyl-4-(4-methylpiperazin-1-yl)phenyl)amino)pyrimidin-4-yl)amino)propyl)-N,1-dimethylazetidine-3-carboxamide, N-(3-((2-((2-bromo-4-(4-methylpiperazin-1-yl)phenyl)amino)-5-(trifluoromethyl)pyrimidin-4-yl)amino)propyl)cyclobutanecarboxamide, N-(3-((2-((2-bromo-4-((1R,5S)-8-methyl-3,8-diazabicyclo[3.2.1]octan-3-yl)phenyl)amino)-5-(trifluoromethyl)pyrimidin-4-yl)amino)propyl)cyclobutanecarboxamide, N-(3-((2-((2-bromo-4-(5-methyl-2,5-diazabicyclo[2.2.1]heptan-2-yl)phenyl)amino)-5-(trifluoromethyl)pyrimidin-4-yl)amino)propyl)cyclobutanecarboxamide, N-(3-((2-((4-(1,4-diazabicyclo[3.2.1]octan-4-

yl)-2-bromophenyl)amino)-5-(trifluoromethyl)pyrimidin-4-yl)amino)propyl)cyclobutanecarboxamide, N-(3-((2-((2-bromo-4-(hexahydropyrrolo[1,2-a]pyrazin-2(1H)-yl)phenyl)amino)-5-(trifluoromethyl)pyrimidin-4-yl)amino)propyl)cyclobutanecarboxamide, N-(3-((2-((2-bromo-4-(4-methylpiperazin-1-yl)phenyl)amino)-5-(difluoromethyl)pyrimidin-4-yl)amino)propyl)cyclobutanecarboxamide, N-(3-((2-((2-chloro-4-(4-methylpiperazin-1-yl)phenyl)amino)-5-(trifluoromethyl)pyrimidin-4-yl)amino)propyl)cyclobutanecarboxamide, N-(3-((2-((2-chloro-4-((1R,5S)-8-methyl-3,8-diazabicyclo[3.2.1]octan-3-yl)phenyl)amino)-5-(trifluoromethyl)pyrimidin-4-yl)amino)propyl)cyclobutanecarboxamide, N-(3-((2-((2-chloro-4-(5-methyl-2,5-diazabicyclo[2.2.1]heptan-2-yl)phenyl)amino)-5-(trifluoromethyl)pyrimidin-4-yl)amino)propyl)cyclobutanecarboxamide, N-(3-((2-((4-(1,4-diazabicyclo[3.2.1]octan-4-yl)-2-chlorophenyl)amino)-5-(trifluoromethyl)pyrimidin-4-yl)amino)propyl)cyclobutanecarboxamide, N-(3-((2-((2-chloro-4-(hexahydropyrrolo[1,2-a]pyrazin-2(1H)-yl)phenyl)amino)-5-(trifluoromethyl)pyrimidin-4-yl)amino)propyl)cyclobutanecarboxamide, N-(3-((2-((2-chloro-4-(4-methylpiperazin-1-yl)phenyl)amino)-5-(difluoromethyl)pyrimidin-4-yl)amino)propyl)cyclobutanecarboxamide, N-(3-((2-((2-cyano-4-(4-methylpiperazin-1-yl)phenyl)amino)-5-(trifluoromethyl)pyrimidin-4-yl)amino)propyl)cyclobutanecarboxamide, N-(3-((2-((2-cyano-4-(4-methylpiperazin-1-yl)phenyl)amino)-5-(difluoromethyl)pyrimidin-4-yl)amino)propyl)cyclobutanecarboxamide, N-(3-((2-((4-(4-methylpiperazin-1-yl)-2-(trifluoromethyl)phenyl)amino)-5-(trifluoromethyl)pyrimidin-4-yl)amino)propyl)cyclobutanecarboxamide, N-(3-((2-((2-(difluoromethyl)-4-(4-methylpiperazin-1-yl)phenyl)amino)-5-(trifluoromethyl)pyrimidin-4-yl)amino)propyl)cyclobutanecarboxamide, N-(3-((2-((2-cyclopropyl-4-(4-methylpiperazin-1-yl)phenyl)amino)-5-(difluoromethyl)pyrimidin-4-yl)amino)propyl)cyclobutanecarboxamide, N-(3-((2-((2-ethyl-4-(4-methylpiperazin-1-yl)phenyl)amino)-5-(trifluoromethyl)pyridin-4-yl)amino)propyl)cyclobutanecarboxamide, N-(3-((2-((2-ethyl-4-(4-methylpiperazin-1-yl)phenyl)amino)-5-(trifluoromethyl)pyridin-4-yl)amino)propyl)-N-methylcyclobutanecarboxamide, N-(3-((5-chloro-2-((2-ethyl-4-(4-methylpiperazin-1-yl)phenyl)amino)pyridin-4-yl)amino)propyl)cyclobutanecarboxamide, N-(3-((5-bromo-2-((2-ethyl-4-(4-methylpiperazin-1-yl)phenyl)amino)pyridin-4-yl)amino)propyl)cyclobutanecarboxamide, N-(3-((5-(difluoromethyl)-2-((2-ethyl-4-(4-methylpiperazin-1-yl)phenyl)amino)pyridin-4-yl)amino)propyl)cyclobutanecarboxamide, N-(3-((2-((2-ethyl-4-(4-methylpiperazin-1-yl)phenyl)amino)-5-(trifluoromethyl)pyrimidin-4-yl)amino)propyl)azetidine-1-carboxamide, N-(3-((2-((2-ethyl-4-(4-methylpiperazin-1-

yl)phenyl)amino)-5-(trifluoromethyl)pyrimidin-4-yl)amino)propyl)-N-methylazetidine-1-carboxamide, 3-(3-((2-((2-ethyl-4-((1R,5S)-8-methyl-3,8-diazabicyclo[3.2.1]octan-3-yl)phenyl)amino)-5-(trifluoromethyl)pyrimidin-4-yl)amino)propyl)-1,1-dimethylurea, 1-(3-((2-((2-ethyl-4-((1R,5S)-8-methyl-3,8-diazabicyclo[3.2.1]octan-3-yl)phenyl)amino)-5-(trifluoromethyl)pyrimidin-4-yl)amino)propyl)-1,3,3-trimethylurea, N-(3-((5-bromo-2-((2-ethyl-4-(4-methylpiperazin-1-yl)phenyl)amino)pyrimidin-4-yl)amino)propyl)azetidine-1-carboxamide, N-(3-((5-bromo-2-((2-ethyl-4-(4-methylpiperazin-1-yl)phenyl)amino)pyrimidin-4-yl)amino)propyl)pyrrolidine-1-carboxamide, N-(3-((2-((2-ethyl-4-(4-methylpiperazin-1-yl)phenyl)amino)-5-(trifluoromethyl)pyrimidin-4-yl)amino)propyl)-3,3-dimethylazetidine-1-carboxamide, 3-(3-((2-((2-ethyl-4-(4-methylpiperazin-1-yl)phenyl)amino)-5-(trifluoromethyl)pyrimidin-4-yl)amino)propyl)-1,1-dimethylurea, N-(3-((2-((2-ethyl-4-(4-methylpiperazin-1-yl)phenyl)amino)-5-(trifluoromethyl)pyrimidin-4-yl)amino)propyl)-2,2-dimethylazetidine-1-carboxamide, 3-(3-((2-((2-ethyl-4-(4-methylpiperazin-1-yl)phenyl)amino)-5-(trifluoromethyl)pyridin-4-yl)amino)propyl)-1,1-dimethylurea, 1-(3-((2-((2-ethyl-4-(4-methylpiperazin-1-yl)phenyl)amino)-5-(trifluoromethyl)pyridin-4-yl)amino)propyl)-1,3,3-trimethylurea, N-(3-((2-((3-methyl-1-(1-methylpiperidin-4-yl)-1H-pyrazol-4-yl)amino)-5-(trifluoromethyl)pyrimidin-4-yl)amino)propyl)cyclobutanecarboxamide, N-(3-((2-((1-(2-(dimethylamino)ethyl)-3-methyl-1H-pyrazol-4-yl)amino)-5-(trifluoromethyl)pyrimidin-4-yl)amino)propyl)cyclobutanecarboxamide, N-(3-((2-((3-methyl-1-(1-methylpyrrolidin-3-yl)-1H-pyrazol-4-yl)amino)-5-(trifluoromethyl)pyrimidin-4-yl)amino)propyl)cyclobutanecarboxamide, N-(3-((5-bromo-2-((3-methyl-1-(1-methylpiperidin-4-yl)-1H-pyrazol-4-yl)amino)pyrimidin-4-yl)amino)propyl)cyclobutanecarboxamide, N-(3-((5-chloro-2-((3-methyl-1-(1-methylpiperidin-4-yl)-1H-pyrazol-4-yl)amino)pyrimidin-4-yl)amino)propyl)cyclobutanecarboxamide, N-(3-((2-((3-methyl-1-(1-methylpiperidin-4-yl)-1H-pyrazol-4-yl)amino)-5-(trifluoromethyl)pyrimidin-4-yl)amino)propyl)tetrahydrofuran-3-carboxamide, N-methyl-N-(3-((2-((3-methyl-1-(1-methylpiperidin-4-yl)-1H-pyrazol-4-yl)amino)-5-(trifluoromethyl)pyrimidin-4-yl)amino)propyl)cyclobutanecarboxamide, N-(3-((5-bromo-2-((3-methyl-1-(1-methylpiperidin-4-yl)-1H-pyrazol-4-yl)amino)pyrimidin-4-yl)amino)propyl)-N-methylcyclobutanecarboxamide, N-(3-((5-chloro-2-((3-methyl-1-(1-methylpiperidin-4-yl)-1H-pyrazol-4-yl)amino)pyrimidin-4-yl)amino)propyl)-N-methylcyclobutanecarboxamide, N-(3-((2-((3-methyl-1-(1-methylpiperidin-4-yl)-1H-pyrazol-4-yl)amino)-5-(trifluoromethyl)pyrimidin-4-yl)amino)propyl)tetrahydro-2H-pyran-4-

carboxamide, N-(3-((2-((3-methyl-1-(1-methylpiperidin-4-yl)-1H-pyrazol-4-yl)amino)-5-(trifluoromethyl)pyrimidin-4-yl)amino)propyl)oxetane-3-carboxamide, N-(3-((2-((1-(2-(dimethylamino)ethyl)-3-methyl-1H-pyrazol-4-yl)amino)-5-(trifluoromethyl)pyrimidin-4-yl)amino)propyl)oxetane-3-carboxamide, N-(3-((2-((3-methyl-1-(1-methylpyrrolidin-3-yl)-1H-pyrazol-4-yl)amino)-5-(trifluoromethyl)pyrimidin-4-yl)amino)propyl)oxetane-3-carboxamide, N-methyl-N-(3-((2-((3-methyl-1-(1-methylpiperidin-4-yl)-1H-pyrazol-4-yl)amino)-5-(trifluoromethyl)pyrimidin-4-yl)amino)propyl)oxetane-3-carboxamide, N-(3-((2-((1-(2-(dimethylamino)ethyl)-3-methyl-1H-pyrazol-4-yl)amino)-5-(trifluoromethyl)pyrimidin-4-yl)amino)propyl)-N-methyloxetane-3-carboxamide, N-methyl-N-(3-((2-((3-methyl-1-(1-methylpyrrolidin-3-yl)-1H-pyrazol-4-yl)amino)-5-(trifluoromethyl)pyrimidin-4-yl)amino)propyl)oxetane-3-carboxamide, N-(3-((5-bromo-2-((3-methyl-1-(1-methylpiperidin-4-yl)-1H-pyrazol-4-yl)amino)pyrimidin-4-yl)amino)propyl)oxetane-3-carboxamide, 1-methyl-N-(3-((2-((3-methyl-1-(1-methylpiperidin-4-yl)-1H-pyrazol-4-yl)amino)-5-(trifluoromethyl)pyrimidin-4-yl)amino)propyl)azetidine-3-carboxamide, N-(3-((2-((1-(2-(dimethylamino)ethyl)-3-methyl-1H-pyrazol-4-yl)amino)-5-(trifluoromethyl)pyrimidin-4-yl)amino)propyl)-1-methylazetidine-3-carboxamide, 1-methyl-N-(3-((2-((3-methyl-1-(1-methylpyrrolidin-3-yl)-1H-pyrazol-4-yl)amino)-5-(trifluoromethyl)pyrimidin-4-yl)amino)propyl)azetidine-3-carboxamide, N,1-dimethyl-N-(3-((2-((3-methyl-1-(1-methylpiperidin-4-yl)-1H-pyrazol-4-yl)amino)-5-(trifluoromethyl)pyrimidin-4-yl)amino)propyl)azetidine-3-carboxamide, N-(3-((2-((1-(2-(dimethylamino)ethyl)-3-methyl-1H-pyrazol-4-yl)amino)-5-(trifluoromethyl)pyrimidin-4-yl)amino)propyl)-N,1-dimethylazetidine-3-carboxamide, N,1-dimethyl-N-(3-((2-((3-methyl-1-(1-methylpyrrolidin-3-yl)-1H-pyrazol-4-yl)amino)-5-(trifluoromethyl)pyrimidin-4-yl)amino)propyl)azetidine-3-carboxamide, N-(3-((5-bromo-2-((3-methyl-1-(1-methylpiperidin-4-yl)-1H-pyrazol-4-yl)amino)pyrimidin-4-yl)amino)propyl)-1-methylazetidine-3-carboxamide, N-(3-((5-(difluoromethyl)-2-((3-methyl-1-(1-methylpiperidin-4-yl)-1H-pyrazol-4-yl)amino)pyrimidin-4-yl)amino)propyl)cyclobutanecarboxamide, N-(3-((5-(difluoromethyl)-2-((3-methyl-1-(1-methylpiperidin-4-yl)-1H-pyrazol-4-yl)amino)pyrimidin-4-yl)amino)propyl)-N-methylcyclobutanecarboxamide, N-(3-((5-(difluoromethyl)-2-((3-methyl-1-(1-methylpiperidin-4-yl)-1H-pyrazol-4-yl)amino)pyrimidin-4-yl)amino)propyl)oxetane-3-carboxamide, N-(3-((5-(difluoromethyl)-2-((3-methyl-1-(1-methylpiperidin-4-yl)-1H-pyrazol-4-yl)amino)pyrimidin-4-yl)amino)propyl)-1-methylazetidine-3-carboxamide, N-(3-((2-((3-methyl-1-(8-methyl-8-azabicyclo[3.2.1]octan-3-yl)-1H-pyrazol-4-yl)amino)-5-

(trifluoromethyl)pyrimidin-4-yl)amino)propyl)cyclobutanecarboxamide, N-methyl-N-(3-((2-((3-methyl-1-(8-methyl-8-azabicyclo[3.2.1]octan-3-yl)-1H-pyrazol-4-yl)amino)-5-(trifluoromethyl)pyrimidin-4-yl)amino)propyl)cyclobutanecarboxamide, N-(3-((2-((3-methyl-1-(8-methyl-8-azabicyclo[3.2.1]octan-3-yl)-1H-pyrazol-4-yl)amino)-5-(trifluoromethyl)pyrimidin-4-yl)amino)propyl)oxetane-3-carboxamide, N-methyl-N-(3-((2-((3-methyl-1-(8-methyl-8-azabicyclo[3.2.1]octan-3-yl)-1H-pyrazol-4-yl)amino)-5-(trifluoromethyl)pyrimidin-4-yl)amino)propyl)oxetane-3-carboxamide, 1-methyl-N-(3-((2-((3-methyl-1-(8-methyl-8-azabicyclo[3.2.1]octan-3-yl)-1H-pyrazol-4-yl)amino)-5-(trifluoromethyl)pyrimidin-4-yl)amino)propyl)azetidine-3-carboxamide, N,1-dimethyl-N-(3-((2-((3-methyl-1-(8-methyl-8-azabicyclo[3.2.1]octan-3-yl)-1H-pyrazol-4-yl)amino)-5-(trifluoromethyl)pyrimidin-4-yl)amino)propyl)azetidine-3-carboxamide, N-(3-((5-(difluoromethyl)-2-((3-methyl-1-(8-methyl-8-azabicyclo[3.2.1]octan-3-yl)-1H-pyrazol-4-yl)amino)pyrimidin-4-yl)amino)propyl)cyclobutanecarboxamide, N-(3-((5-(difluoromethyl)-2-((3-methyl-1-(8-methyl-8-azabicyclo[3.2.1]octan-3-yl)-1H-pyrazol-4-yl)amino)pyrimidin-4-yl)amino)propyl)oxetane-3-carboxamide, N-(3-((5-(difluoromethyl)-2-((3-methyl-1-(8-methyl-8-azabicyclo[3.2.1]octan-3-yl)-1H-pyrazol-4-yl)amino)pyrimidin-4-yl)amino)propyl)-1-methylazetidine-3-carboxamide, N-(3-((5-bromo-2-((3-methyl-1-(8-methyl-8-azabicyclo[3.2.1]octan-3-yl)-1H-pyrazol-4-yl)amino)pyrimidin-4-yl)amino)propyl)cyclobutanecarboxamide, N-(3-((5-bromo-2-((3-methyl-1-(8-methyl-8-azabicyclo[3.2.1]octan-3-yl)-1H-pyrazol-4-yl)amino)pyrimidin-4-yl)amino)propyl)oxetane-3-carboxamide, N-(3-((5-bromo-2-((3-methyl-1-(8-methyl-8-azabicyclo[3.2.1]octan-3-yl)-1H-pyrazol-4-yl)amino)pyrimidin-4-yl)amino)propyl)-1-methylazetidine-3-carboxamide, N-(3-((5-chloro-2-((3-methyl-1-(8-methyl-8-azabicyclo[3.2.1]octan-3-yl)-1H-pyrazol-4-yl)amino)pyrimidin-4-yl)amino)propyl)cyclobutanecarboxamide, N-(3-((5-chloro-2-((3-methyl-1-(8-methyl-8-azabicyclo[3.2.1]octan-3-yl)-1H-pyrazol-4-yl)amino)pyrimidin-4-yl)amino)propyl)oxetane-3-carboxamide, N-(3-((5-chloro-2-((3-methyl-1-(8-methyl-8-azabicyclo[3.2.1]octan-3-yl)-1H-pyrazol-4-yl)amino)pyrimidin-4-yl)amino)propyl)-1-methylazetidine-3-carboxamide, N-(3-((2-((3-methyl-1-(1-methylpiperidin-4-yl)-1H-pyrazol-4-yl)amino)-5-(trifluoromethyl)pyrimidin-4-yl)amino)propyl)isobutyramide, N-(3-((2-((3-methyl-1-(1-methylpiperidin-4-yl)-1H-pyrazol-4-yl)amino)-5-(trifluoromethyl)pyrimidin-4-yl)amino)propyl)pivalamide, N-methyl-N-(3-((2-((3-methyl-1-(1-methylpiperidin-4-yl)-1H-pyrazol-4-yl)amino)-5-(trifluoromethyl)pyrimidin-4-yl)amino)propyl)pivalamide, N-(3-((5-bromo-2-((3-methyl-1-(1-methylpiperidin-4-yl)-1H-pyrazol-4-yl)amino)pyrimidin-4-yl)amino)propyl)pivalamide, N-(3-((5-bromo-2-((3-methyl-1-(8-methyl-8-

azabicyclo[3.2.1]octan-3-yl)-1H-pyrazol-4-yl)amino)pyrimidin-4-yl)amino)propyl)pivalamide, 3,3-difluoro-N-(3-((2-((3-methyl-1-(1-methylpiperidin-4-yl)-1H-pyrazol-4-yl)amino)-5-(trifluoromethyl)pyrimidin-4-yl)amino)propyl)cyclobutane-1-carboxamide, 3,3-difluoro-N-(3-((2-((3-methyl-1-(8-methyl-8-azabicyclo[3.2.1]octan-3-yl)-1H-pyrazol-4-yl)amino)-5-(trifluoromethyl)pyrimidin-4-yl)amino)propyl)cyclobutane-1-carboxamide, 3,3-difluoro-N-methyl-N-(3-((2-((3-methyl-1-(1-methylpiperidin-4-yl)-1H-pyrazol-4-yl)amino)-5-(trifluoromethyl)pyrimidin-4-yl)amino)propyl)cyclobutane-1-carboxamide, 3,3-difluoro-N-methyl-N-(3-((2-((3-methyl-1-(8-methyl-8-azabicyclo[3.2.1]octan-3-yl)-1H-pyrazol-4-yl)amino)-5-(trifluoromethyl)pyrimidin-4-yl)amino)propyl)cyclobutane-1-carboxamide, N-(3-((5-(difluoromethyl)-2-((3-methyl-1-(1-methylpiperidin-4-yl)-1H-pyrazol-4-yl)amino)pyrimidin-4-yl)amino)propyl)-3,3-difluorocyclobutane-1-carboxamide, N-(3-((5-bromo-2-((3-methyl-1-(1-methylpiperidin-4-yl)-1H-pyrazol-4-yl)amino)pyrimidin-4-yl)amino)propyl)-3,3-difluorocyclobutane-1-carboxamide, N-(3-((5-bromo-2-((3-methyl-1-(8-methyl-8-azabicyclo[3.2.1]octan-3-yl)-1H-pyrazol-4-yl)amino)pyrimidin-4-yl)amino)propyl)-3,3-difluorocyclobutane-1-carboxamide, N-(3-((5-chloro-2-((3-methyl-1-(1-methylpiperidin-4-yl)-1H-pyrazol-4-yl)amino)pyrimidin-4-yl)amino)propyl)-3,3-difluorocyclobutane-1-carboxamide, N-(3-((2-((5-methyl-1-(1-methylpiperidin-4-yl)-1H-1,2,3-triazol-4-yl)amino)-5-(trifluoromethyl)pyrimidin-4-yl)amino)propyl)cyclobutanecarboxamide, N-(3-((2-((5-methyl-2-(1-methylpiperidin-4-yl)-2H-1,2,3-triazol-4-yl)amino)-5-(trifluoromethyl)pyrimidin-4-yl)amino)propyl)cyclobutanecarboxamide, N-(3-((2-((5-methyl-2-(1-methylpiperidin-4-yl)thiazol-4-yl)amino)-5-(trifluoromethyl)pyrimidin-4-yl)amino)propyl)cyclobutanecarboxamide, N-(3-((2-((5-methyl-2-(1-methylpiperidin-4-yl)oxazol-4-yl)amino)-5-(trifluoromethyl)pyrimidin-4-yl)amino)propyl)cyclobutanecarboxamide, N-(3-((2-((4-methyl-2-(1-methylpiperidin-4-yl)thiazol-5-yl)amino)-5-(trifluoromethyl)pyrimidin-4-yl)amino)propyl)cyclobutanecarboxamide, N-(3-((2-((4-methyl-2-(1-methylpiperidin-4-yl)oxazol-5-yl)amino)-5-(trifluoromethyl)pyrimidin-4-yl)amino)propyl)cyclobutanecarboxamide, N-(3-((2-((5-methyl-2-(4-methylpiperazin-1-yl)thiazol-4-yl)amino)-5-(trifluoromethyl)pyrimidin-4-yl)amino)propyl)cyclobutanecarboxamide, N-(3-((2-((5-methyl-2-(4-methylpiperazin-1-yl)oxazol-4-yl)amino)-5-(trifluoromethyl)pyrimidin-4-yl)amino)propyl)cyclobutanecarboxamide, N-(3-((2-((4-methyl-2-(4-methylpiperazin-1-yl)thiazol-5-yl)amino)-5-(trifluoromethyl)pyrimidin-4-

yl)amino)propyl)cyclobutanecarboxamide, N-(3-((2-((4-methyl-2-(4-methylpiperazin-1-yl)oxazol-5-yl)amino)-5-(trifluoromethyl)pyrimidin-4-yl)amino)propyl)cyclobutanecarboxamide, N-(3-((2-((5-methyl-1-(1-methylpiperidin-4-yl)-1H-1,2,3-triazol-4-yl)amino)-5-(trifluoromethyl)pyrimidin-4-yl)amino)propyl)oxetane-3-carboxamide, N-(3-((2-((5-methyl-2-(1-methylpiperidin-4-yl)-2H-1,2,3-triazol-4-yl)amino)-5-(trifluoromethyl)pyrimidin-4-yl)amino)propyl)oxetane-3-carboxamide, N-(3-((2-((5-methyl-2-(1-methylpiperidin-4-yl)thiazol-4-yl)amino)-5-(trifluoromethyl)pyrimidin-4-yl)amino)propyl)oxetane-3-carboxamide, N-(3-((2-((5-methyl-2-(1-methylpiperidin-4-yl)oxazol-4-yl)amino)-5-(trifluoromethyl)pyrimidin-4-yl)amino)propyl)oxetane-3-carboxamide, N-(3-((2-((4-methyl-2-(1-methylpiperidin-4-yl)thiazol-5-yl)amino)-5-(trifluoromethyl)pyrimidin-4-yl)amino)propyl)oxetane-3-carboxamide, N-(3-((2-((4-methyl-2-(1-methylpiperidin-4-yl)oxazol-5-yl)amino)-5-(trifluoromethyl)pyrimidin-4-yl)amino)propyl)oxetane-3-carboxamide, N-(3-((2-((5-methyl-2-(4-methylpiperazin-1-yl)thiazol-4-yl)amino)-5-(trifluoromethyl)pyrimidin-4-yl)amino)propyl)oxetane-3-carboxamide, N-(3-((2-((5-methyl-2-(4-methylpiperazin-1-yl)oxazol-4-yl)amino)-5-(trifluoromethyl)pyrimidin-4-yl)amino)propyl)oxetane-3-carboxamide, N-(3-((2-((4-methyl-2-(4-methylpiperazin-1-yl)thiazol-5-yl)amino)-5-(trifluoromethyl)pyrimidin-4-yl)amino)propyl)oxetane-3-carboxamide, N-(3-((2-((4-methyl-2-(4-methylpiperazin-1-yl)oxazol-5-yl)amino)-5-(trifluoromethyl)pyrimidin-4-yl)amino)propyl)oxetane-3-carboxamide, 3,3-difluoro-N-(3-((2-((5-methyl-2-(1-methylpiperidin-4-yl)-2H-1,2,3-triazol-4-yl)amino)-5-(trifluoromethyl)pyrimidin-4-yl)amino)propyl)cyclobutane-1-carboxamide, 1-methyl-N-(3-((2-((5-methyl-1-(1-methylpiperidin-4-yl)-1H-1,2,3-triazol-4-yl)amino)-5-(trifluoromethyl)pyrimidin-4-yl)amino)propyl)azetidine-3-carboxamide, 1-methyl-N-(3-((2-((5-methyl-2-(1-methylpiperidin-4-yl)-2H-1,2,3-triazol-4-yl)amino)-5-(trifluoromethyl)pyrimidin-4-yl)amino)propyl)azetidine-3-carboxamide, 1-methyl-N-(3-((2-((5-methyl-2-(1-methylpiperidin-4-yl)thiazol-4-yl)amino)-5-(trifluoromethyl)pyrimidin-4-yl)amino)propyl)azetidine-3-carboxamide, 1-methyl-N-(3-((2-((5-methyl-2-(1-methylpiperidin-4-yl)oxazol-4-yl)amino)-5-(trifluoromethyl)pyrimidin-4-yl)amino)propyl)azetidine-3-carboxamide, 1-methyl-N-(3-((2-((4-methyl-2-(1-methylpiperidin-4-yl)thiazol-5-yl)amino)-5-(trifluoromethyl)pyrimidin-4-yl)amino)propyl)azetidine-3-carboxamide, 1-methyl-N-(3-((2-((4-methyl-2-(1-methylpiperidin-4-yl)oxazol-5-yl)amino)-5-(trifluoromethyl)pyrimidin-4-yl)amino)propyl)azetidine-3-carboxamide, 1-methyl-N-(3-((2-((5-methyl-2-(4-methylpiperazin-1-yl)thiazol-4-yl)amino)-5-(trifluoromethyl)pyrimidin-4-

yl)amino)propyl)azetidine-3-carboxamide, 1-methyl-N-(3-((2-((5-methyl-2-(4-methylpiperazin-1-yl)oxazol-4-yl)amino)-5-(trifluoromethyl)pyrimidin-4-yl)amino)propyl)azetidine-3-carboxamide, 1-methyl-N-(3-((2-((4-methyl-2-(4-methylpiperazin-1-yl)thiazol-5-yl)amino)-5-(trifluoromethyl)pyrimidin-4-yl)amino)propyl)azetidine-3-carboxamide, 1-methyl-N-(3-((2-((4-methyl-2-(4-methylpiperazin-1-yl)oxazol-5-yl)amino)-5-(trifluoromethyl)pyrimidin-4-yl)amino)propyl)azetidine-3-carboxamide, N-(3-((2-((5-methyl-2-(1-methylpiperidin-4-yl)-2H-1,2,3-triazol-4-yl)amino)-5-(trifluoromethyl)pyridin-4-yl)amino)propyl)cyclobutanecarboxamide, N-(3-((2-((5-methyl-2-(1-methylpiperidin-4-yl)thiazol-4-yl)amino)-5-(trifluoromethyl)pyridin-4-yl)amino)propyl)cyclobutanecarboxamide, N-(3-((2-((5-methyl-2-(1-methylpiperidin-4-yl)oxazol-4-yl)amino)-5-(trifluoromethyl)pyridin-4-yl)amino)propyl)cyclobutanecarboxamide, N-(3-((2-((4-methyl-2-(1-methylpiperidin-4-yl)thiazol-5-yl)amino)-5-(trifluoromethyl)pyridin-4-yl)amino)propyl)cyclobutanecarboxamide, N-(3-((2-((4-methyl-2-(1-methylpiperidin-4-yl)oxazol-5-yl)amino)-5-(trifluoromethyl)pyridin-4-yl)amino)propyl)cyclobutanecarboxamide, N-(3-((2-((3-methyl-1-(1-methylpiperidin-4-yl)-1H-pyrazol-4-yl)amino)-5-(trifluoromethyl)pyridin-4-yl)amino)propyl)cyclobutanecarboxamide, N-methyl-N-(3-((2-((3-methyl-1-(1-methylpiperidin-4-yl)-1H-pyrazol-4-yl)amino)-5-(trifluoromethyl)pyridin-4-yl)amino)propyl)cyclobutanecarboxamide, N-(3-((2-((3-methyl-1-(1-methylpiperidin-4-yl)-1H-pyrazol-4-yl)amino)-5-(trifluoromethyl)pyridin-4-yl)amino)propyl)oxetane-3-carboxamide, 1-methyl-N-(3-((2-((3-methyl-1-(1-methylpiperidin-4-yl)-1H-pyrazol-4-yl)amino)-5-(trifluoromethyl)pyridin-4-yl)amino)propyl)azetidine-3-carboxamide, N-(3-((2-((3-methyl-1-(8-methyl-8-azabicyclo[3.2.1]octan-3-yl)-1H-pyrazol-4-yl)amino)-5-(trifluoromethyl)pyridin-4-yl)amino)propyl)cyclobutanecarboxamide, N-(3-((2-((3-methyl-1-(8-methyl-8-azabicyclo[3.2.1]octan-3-yl)-1H-pyrazol-4-yl)amino)-5-(trifluoromethyl)pyridin-4-yl)amino)propyl)oxetane-3-carboxamide, 1-methyl-N-(3-((2-((3-methyl-1-(8-methyl-8-azabicyclo[3.2.1]octan-3-yl)-1H-pyrazol-4-yl)amino)-5-(trifluoromethyl)pyridin-4-yl)amino)propyl)azetidine-3-carboxamide, N-(3-((2-((3-methyl-1-(1-methylpiperidin-4-yl)-1H-pyrazol-4-yl)amino)-5-(trifluoromethyl)pyrimidin-4-yl)amino)propyl)azetidine-1-carboxamide, 1,1-dimethyl-3-(3-((2-((3-methyl-1-(1-methylpiperidin-4-yl)-1H-pyrazol-4-yl)amino)-5-(trifluoromethyl)pyrimidin-4-yl)amino)propyl)urea, N-methyl-N-(3-((2-((3-methyl-1-(1-methylpiperidin-4-yl)-1H-pyrazol-

4-yl)amino)-5-(trifluoromethyl)pyrimidin-4-yl)amino)propyl)azetidine-1-carboxamide, 1,1,3-trimethyl-3-(3-((2-((3-methyl-1-(1-methylpiperidin-4-yl)-1H-pyrazol-4-yl)amino)-5-(trifluoromethyl)pyrimidin-4-yl)amino)propyl)urea, and pharmaceutically acceptable salts, enantiomers, stereoisomers, and tautomers thereof.

~~65~~15. A pharmaceutical composition comprising a compound of any one of claims 1-~~64~~ 14 and a pharmaceutically acceptable excipient.

~~66~~16. A pharmaceutical composition comprising a compound of any one of claims 1-~~64~~14, one or more additional therapeutic agents, and a pharmaceutically acceptable excipient.

~~67~~17. The pharmaceutical composition of claim ~~66~~16, wherein the composition comprises one additional therapeutic agent.

18~~68~~. The pharmaceutical composition of claim ~~66~~ 16 or claim ~~67~~17, wherein the additional therapeutic agent is a MAPKAP pathway inhibitor.

~~69~~19. The pharmaceutical composition of claim ~~68~~18, wherein the MAPKAP pathway inhibitor is selected from the group consisting of a MEK inhibitor, an ERK inhibitor, a RAF inhibitor, and a Ras inhibitor.

2~~7~~0. The pharmaceutical composition of claim ~~69~~19, wherein the MEK inhibitor is selected from the group consisting of trametinib, selumetinib, cobimetinib, binimetinib, and pharmaceutically acceptable salts thereof; ~~.~~

~~71. The pharmaceutical composition of claim 69, wherein~~ the ERK inhibitor is selected from the group consisting of ulixertinib, SCH772984, LY3214996, ravoxertinib, VX-11e, and pharmaceutically acceptable salts thereof; ~~.~~

~~72. The pharmaceutical composition of claim 69, wherein~~ the RAF inhibitor is selected from the group consisting of LY3009120, LXH254, RAF709, dabrafenib, vemurafenib, and pharmaceutically acceptable salts thereof; or ~~.~~

~~73. The pharmaceutical composition of claim 69, wherein~~ the Ras inhibitor is selected from the group consisting of AMG-510, MRTX849, and pharmaceutically acceptable salts thereof.

~~74~~21. The pharmaceutical composition of claim ~~66~~ 16 or claim ~~67~~17, wherein the additional therapeutic agent is a chemotherapeutic agent.

~~75~~22. The pharmaceutical composition of claim ~~74~~21, wherein the chemotherapeutic agent is a selected from the group consisting of anti-tubulin agents, vinorelbine, DNA-alkylating agents, DNA intercalating agents, 5-fluorouracil, capecitabine, cytarabine, decitabine, 5-aza cytadine, gemcitabine, and methotrexate.

~~76~~23. Use of a compound of any one of claims 1-14 in the manufacture of a medicament for ~~A method of~~ treating a tumor in a patient in need thereof~~, comprising administering to the patient a therapeutically effective amount of a compound of any one of claims 1-64~~.

~~77~~24. Use of a compound of any one of claims 1-14 in the manufacture of a medicament for ~~A method of~~ treating a cancer in a patient in need thereof~~, comprising administering to the patient a therapeutically effective amount of a compound of any one of claims 1-64~~.

~~78~~25. The ~~method~~ use of claim ~~77~~24, wherein the cancer is selected from the group consisting of gastrointestinal stromal tumors, esophageal cancer, gastric cancer, melanomas, gliomas, glioblastomas, ovarian cancer, bladder cancer, pancreatic cancer, prostate cancer, lung cancers, breast cancers, renal cancers, hepatic cancers, osteosarcomas, multiple myelomas, cervical carcinomas, cancers that are metastatic to bone, papillary thyroid carcinoma, non-small cell lung cancer, and colorectal cancers.

~~79. The method of claim 77 or claim 78, wherein the cancer is metastatic.~~

~~80. A method of treating a disorder selected from the group consisting of melanomas, glioblastomas, ovarian cancer, pancreatic cancer, prostate cancer, lung cancers, breast cancers, renal cancers, hepatic cancers, osteosarcomas, multiple myelomas, cervical carcinomas, cancers that are metastatic to bone, papillary thyroid carcinoma, non-small cell~~

~~lung cancer, and colonic cancers in a patient in need thereof, comprising administering to the patient a therapeutically effective amount of a compound of any one of claims 1-64.~~

~~81~~26. The use ~~method~~ of ~~any one of claims 76-80~~claim 24 or 25, wherein ~~further comprising administering to the patient~~ one or more additional therapeutic agents is to be administered to the patient.

~~82~~27. The use ~~method~~ of claim ~~81~~26, wherein the additional therapeutic agent is a MAPKAP pathway inhibitor.

~~83~~28. The use ~~method~~ of claim ~~82~~27, wherein the MAPKAP pathway inhibitor is selected from the group consisting of a MEK inhibitor, an ERK inhibitor, a RAF inhibitor, and a Ras inhibitor.

29~~84~~. The use ~~method~~ of claim ~~83~~28, wherein the MEK inhibitor is selected from the group consisting of trametinib, selumetinib, cobimetinib, binimetinib, and pharmaceutically acceptable salts thereof; ~~.~~

~~85. The method of claim 83, wherein~~ the ERK inhibitor is selected from the group consisting of ulixertinib, SCH772984, LY3214996, ravoxertinib, VX-11e, and pharmaceutically acceptable salts thereof; ~~.~~

~~86. The method of claim 83, wherein t~~he RAF inhibitor is selected from the group consisting of LY3009120, LXH254, RAF709, dabrafenib, vemurafenib, and pharmaceutically acceptable salts thereof; ~~.~~

~~87. The method of claim 83, wherein~~oe the Ras inhibitor is selected from the group consisting of AMG-510, MRTX849, and pharmaceutically acceptable salts thereof.

~~88~~30. The use ~~method~~ of claim ~~83~~26, wherein the additional therapeutic agent is a chemotherapeutic agent.

~~89~~31. The use ~~method~~ of claim ~~88~~30, wherein the chemotherapeutic agent is a selected from the group consisting of anti-tubulin agents, vinorelbine, DNA-alkylating agents, DNA

intercalating agents, 5-fluorouracil, capecitabine, cytarabine, decitabine, 5-aza cytadine, gemcitabine, and methotrexate.

32. A compound of any one of claims 1-14 for use in therapy.